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ACUTE NON-SPECIFIC MYOCARDITIS *

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A PECULIARLY anomalous situation exists in present day medicine. A mass of evidence has been collected by the pathologist to justify the recognition of an entity characterized by an acute inflammatory process involving the myocardium and most often secondary to some acute infectious disease, apart from the septicemias and the specific myocarditides occurring in such diseases as rheumatic fever, tuberculosis, and rarely syphilis. He has quite correctly labeled the condition as acute myocarditis. He has also on occasion demonstrated the same process apparently unassociated with any evident primary disease. He frequently decries the fact that the clinician does not make the diagnosis often enough. On the other hand, a mass of evidence has been collected by the internist to show that alterations of the electrocardiogram, from the mildest to the most profound, may and frequently do occur in the course of many acute and occasionally chronic infectious diseases, often in a most unanticipated fashion. If these same electrocardiographic alterations are observed in the course of acute rheumatic fever, in which the pathologic change involving the myocardium is well appreciated, they are accepted almost without exception as evidence of acute rheumatic myocarditis. Yet the vast majority of internists have been loathe to recognize these alterations as evidence of acute myocarditis or have merely overlooked the evidence when it was observed in the course of acute infectious disease, non-rheumatic in origin. The clinician has not been impressed with the significance of the electrocardiographic findings because almost all of these patients recover and practically no autopsy material is available from them to correlate lesions with the clinical observations. The pathologist will examine the myocardium in those who die of an acute infectious disease.

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From these he draws most of his conclusions. Usually the primary disease dominates the picture so much that a finding of myocarditis is interesting but very secondary. If the pathologist has an unusual interest in myocarditis, he is able to collect an appreciable number of cases, as Saphir [1] was able to do in his series of 240 cases in 5,626 autopsies. Sudden death, or death due to progressive myocardial insufficiency, has excited both the pathologist and internist, particularly when there was no history of antecedent disease and no primary disease was evident clinically, while at autopsy nothing but acute myocarditis was demonstrable. A number of such cases have been recorded in the literature under such titles as Fiedler's myocarditis; acute, subacute and chronic isolated myocarditis; acute, subacute, and chronic interstitial myocarditis; idiopathic myocarditis; primary myocarditis.[2, 3, 4, 5, 6, 7, 8, 9, 10]

Hansman and Schenken [5] are of the opinion that acute isolated myocarditis differs etiologically from the acute toxic myocarditis which is caused by infectious disease only in that the origin of the infectious agent is obscure. We concur in this opinion. The cases of acute isolated myocarditis recorded in the literature, although relatively few, are of great importance. They pose the question as to whether or not they represent a particular group of cases of heart disease which always terminates fatally, or whether they represent only some of the fatalities of a larger group of acute myocarditis, nonspecific in nature, in which the majority recover even though they have never been recognized clinically, whereas the minority, likewise not recognized clinically, do not recover and at autopsy show acute myocarditis.

Scherf and Boyd,[11] who have written an excellent account of acute myocarditis, say "the frequency and significance of myocarditis has been evaluated very differently in the course of recent years. There were and at present still are physicians who designate almost every myocardial disease as myocarditis or fibroid myocarditis, providing a valvular lesion is excluded, despite the presence of a definite coronary sclerosis or cardiac failure from an associated hypertension. Against this generalization, a very natural adverse reaction has developed and at many very estimable institutions myocarditis is designated as a rare affection which can be diagnosed clinically only in exceptional cases. Neither attitude is correct. Sufficient evidence has been collected to prove that myocarditis has not been correctly appraised in regard to its importance or frequency. Myocarditis is a common disease and quite often remains unrecognized."

Maher and Wosika [12] have noted "that the frequent association of myocardial injury with acute infections is not as common knowledge as it should be. Injury to the myocardium and the intimately associated conduction system is undoubtedly more frequent than we know."

We wish to record the cases of 11 patients whom we have observed clinically and in whom the clinical diagnosis of acute myocarditis was made. The evidence for the diagnosis is presented. We shall also record a case of sudden death due to acute myocarditis, secondary to an acute suppurative

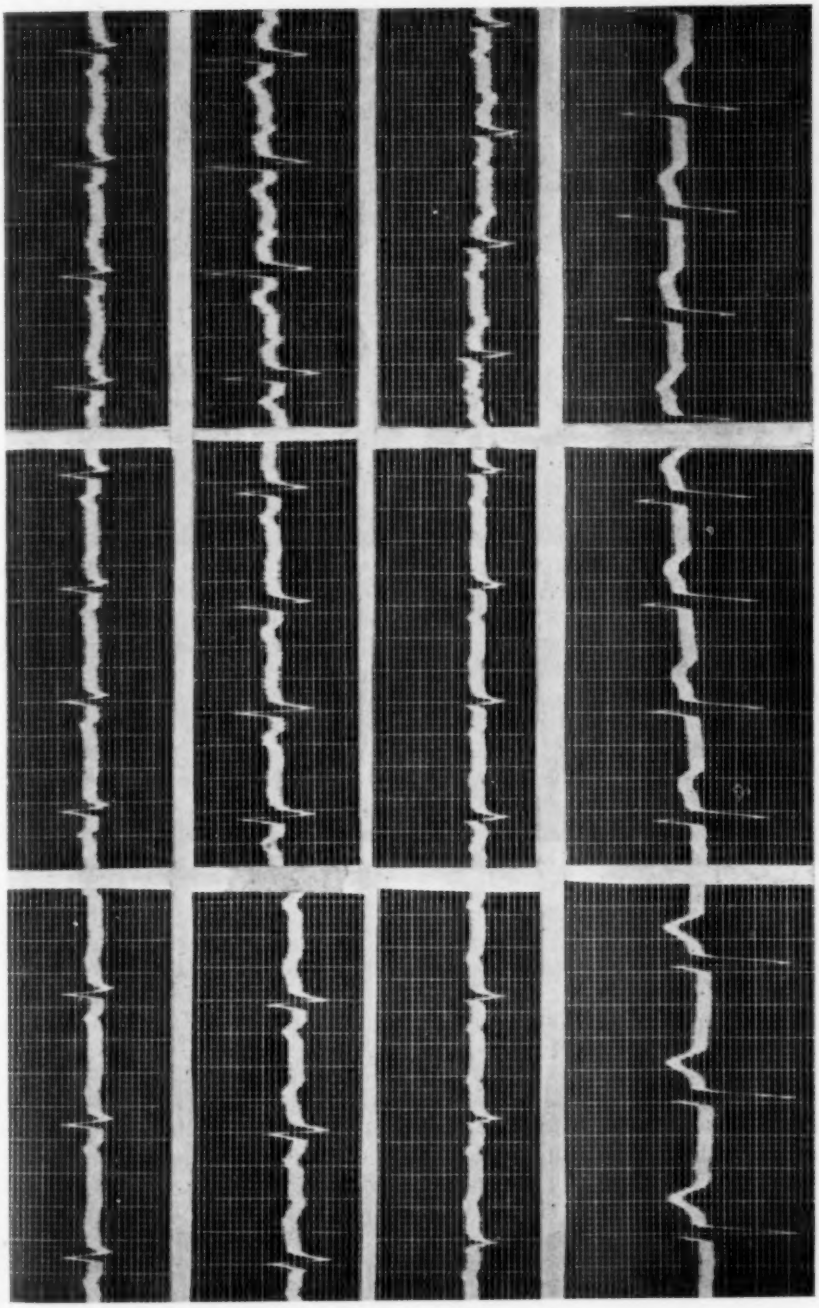


FIG. 1. *Case 1.* Diagnosis: Peritonsillar abscess; acute non-specific myocarditis. Flattening of T_1 and T_2 on second day. Inversion of T-waves in L_2 and L_3 on fifth day.

tonsillitis, which was observed at another institution and autopsied by one of us.

Case Reports

Case 1. Diagnosis: Peritonsillar abscess; acute non-specific myocarditis.

W. P., an officer aged 28 years, complained of difficulty in swallowing for one day. His temperature on admission was 100° F. Examination showed a left peritonsillar abscess which was incised 48 hours after admission. The erythrocyte sedimentation rate on the second day was 25 mm. in one hour (Cutler method). He improved rapidly and was discharged on the sixth day.

Because of the marked toxemia and our academic interest in this instance an electrocardiogram was taken on admission. T_1 was low. There was a left axis deviation (figure 1). On the second day T_1 and T_2 were practically isoelectric and T_4 was lower. On the fifth day T_2 and T_3 became inverted.

Comment: A diagnosis of acute myocarditis was made on these electrocardiographic findings. The officer was returned to duty on the sixth day. This was an obvious error on our part.

Case 2. Diagnosis: Pneumonia, lobar; acute non-specific myocarditis.

J. H., S2c, aged 34 years, was admitted one day after a severe chill, followed by fever, cough, and bloody expectoration. His temperature was 103° F., pulse 88 with extrasystoles, respirations 18, blood pressure 130 mm. Hg systolic and 70 mm. diastolic. There was dullness over the left lower lung posteriorly and numerous crepitant râles were heard. The heart was not enlarged to percussion. There were no murmurs. Gallop rhythm was present. Roentgenogram showed consolidation of the left lower lobe. During the examination the patient felt faint and broke out into a profuse perspiration. An electrocardiogram was taken. It showed bundle branch block (common type) with occasional extrasystoles. He became afebrile on the sixth day but complained of weakness. An electrocardiogram done on that day still showed bundle branch block with variations in QRS and T-waves and a P–R interval of 0.30 second. Subsequent studies showed variations of the dominant bundle branch block and the last electrocardiogram done on the ninety-sixth day still showed the bundle branch block and a P–R interval of 0.30 second (figure 2). The erythrocyte sedimentation rate on admission was 23 mm. (Cutler) in one hour. It remained rapid for 90 days when it fell to 15 mm. per hour.

Comment: It is our opinion that the bundle branch block was probably a consequence of the pneumonia and did not precede it. This is borne out by the fact that the pattern of the electrocardiogram continued to change during the period of observation (see T-wave changes in L_2 and L_3).

Case 3. Diagnosis: Pneumonia, primary atypical, etiology unknown; acute non-specific myocarditis.

W. W. D., S2c, aged 18 years, was first admitted on December 6, 1943 with a history of cough for two weeks, fever and chilliness for one day. He was not acutely ill. Temperature was 102° F. There were a few râles at the left base. Roentgenogram showed a left lower lobe infiltration. His temperature fell to a normal level gradually, and on December 26 it was normal and remained so except for two days when it rose to 99° F. He was discharged to duty on January 18, 1944.

On February 1 the man was seen in consultation because of breathlessness on exertion. Temperature was 98.6° F., pulse 80, blood pressure 124 mm. Hg systolic and 80 mm. diastolic, and respirations 22. Physical examination was negative. The erythrocyte sedimentation rate was 26 mm. in one hour. An electrocardiogram showed a complete A–V dissociation (figure 3). He was admitted to the sick bay where he remained afebrile throughout this admission. A roentgenogram of the chest was negative for pulmonary disease. The heart was normal in size and shape. One week

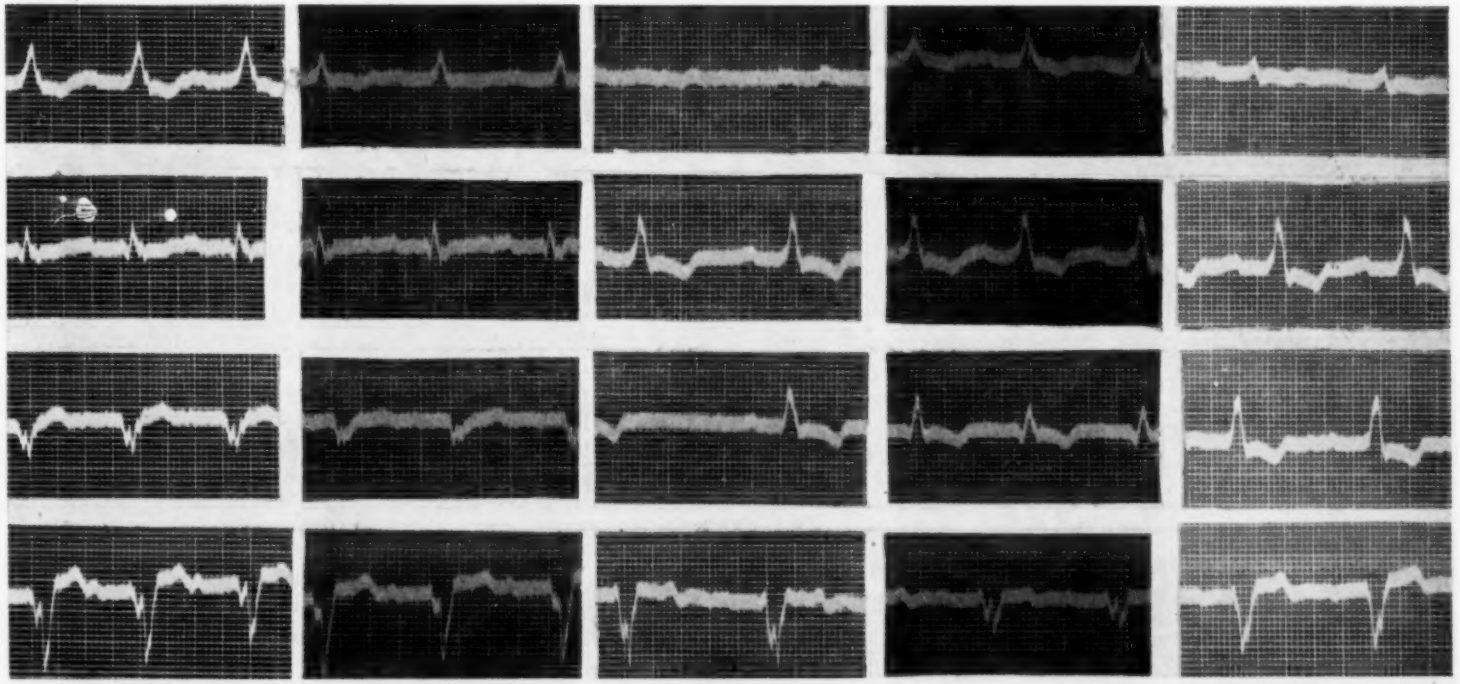


FIG. 2. *Case 2.* Diagnosis: Lobar pneumonia; acute non-specific myocarditis. Electrocardiograms on first and fourth days show bundle branch block, common type. In the three subsequent electrocardiograms, note the variations in direction of QRS_3 and T_3 while QRS_1 in the last two tracings remains upright. The last three tracings are therefore still consistent with diagnosis of bundle branch block, common type.

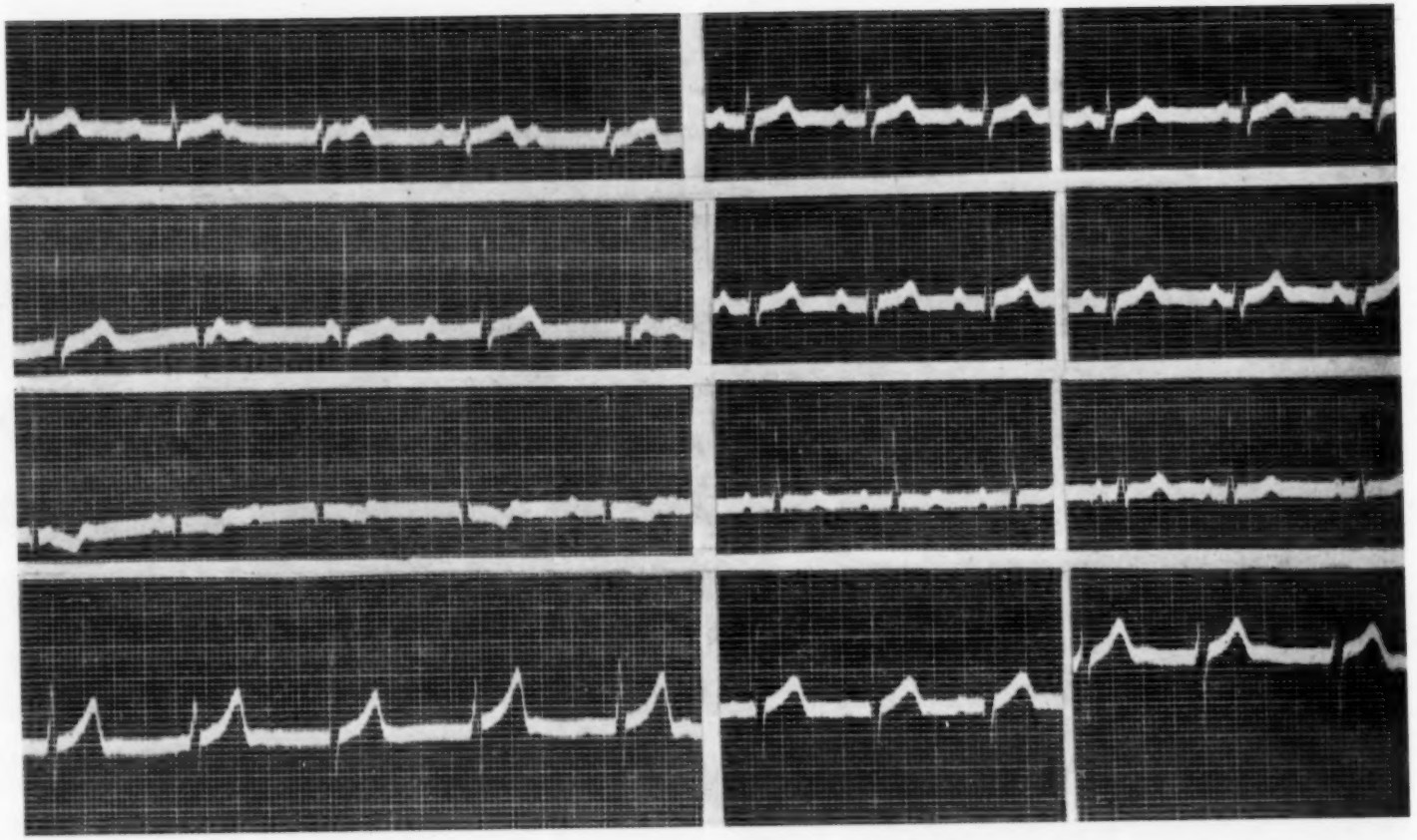


FIG. 3. *Case 3.* Diagnosis: Pneumonia, primary atypical, etiology unknown; acute non-specific myocarditis. Discharged to duty 43 days after admission for pneumonia. Readmitted 14 days later (fifty-seventh day) because of breathlessness. First tracing complete A-V dissociation. Second tracing normal rhythm with P-R interval 0.20 second. Third tracing normal rhythm, P-R interval 0.14 second.

later the electrocardiogram showed a normal rhythm with a P–R interval of 0.20 second. Fifteen days after admission the rhythm was normal and the P–R interval 0.14 second. The erythrocyte sedimentation rate was 23 mm. in one hour on the eighth day and 7 mm. on the thirty-eighth day. He was returned to duty 45 days after this second admission.

Comment: This is an example of acute myocarditis following pneumonia. The symptom of breathlessness, coupled with the suspicion that it might be due to myocarditis following an acute infection, led to the diagnosis.

Case 4. Diagnosis: Scarlet fever; acute non-specific myocarditis.

J. A. S., S2c, aged 18 years, entered the hospital on January 21, 1944 with a sore throat and a typical scarlet fever rash. Temperature was 100.4° F. on admission and rose to 104° on the fourth day. His tonsils were inflamed. The *Streptococcus anhemolyticus*, gamma was cultured from the throat. He developed a cervical lymphadenitis on the fourteenth day. This subsided and he became afebrile on the nineteenth day of disease. On the latter date he began to complain of pains in the knees and ankles. There was no evidence of swelling, no tenderness, and no pain on motion. The erythrocyte sedimentation rate was 28 mm. per hour. The heart was not enlarged. There were no murmurs. An electrocardiogram done on the twenty-third day showed an inverted T_1 and T_4 and a low T_2 (figure 4). Two days later T_2 became almost isoelectric. On the thirty-ninth day T_1 and T_2 were again upright and T_4 was biphasic. On the fifty-seventh day a normal tracing was obtained. Roentgenogram of the chest showed a normal cardiac configuration. The erythrocyte sedimentation rate became normal on the thirty-first day. He was permitted out of bed on the fortieth day and was discharged on the sixty-first.

Comment: This is an example of acute myocarditis following scarlet fever. Our attention was focused on the heart because of the arthralgias and the possibility of a complicating rheumatic infection.

Case 5. Diagnosis: Acute recurrent gonococcal arthritis; acute non-specific myocarditis.

F. G. O., BMlc, aged 38 years, gave a history of gonorrheal urethritis in October 1943. One week after the onset of the urethral discharge, he developed swelling and pain of the left ankle, knee and wrist. He was confined to bed for four weeks and then sent to duty.

The man was later transferred to this activity, where, on March 31, 1944, he was admitted to the sick bay with a story of pain and swelling of the right wrist and ankle for one week. Temperature was 101° F. All findings were negative except for swelling and tenderness of the right wrist and ankle. The erythrocyte sedimentation rate was 25 mm. in one hour. Roentgenogram of the chest showed heart normal in size and shape. He had a low grade fever, not over 100° F., for six weeks. The inflamed joints did not respond to large doses of salicylates or to a course of sulfadiazine. After five weeks, pain, tenderness and swelling of the joints subsided. The wrist and ankle, however, showed much periarticular thickening. An electrocardiogram done on the eleventh day after admission (eighteenth day of disease) showed a low T_1 and an inverted T_4 (figure 5). On the twenty-seventh day of disease T_1 was practically isoelectric. On the thirty-seventh day T_1 was higher and T_4 became positive. The electrocardiogram on the sixty-fourth day showed T_1 to be normal. The sedimentation rate was 26 mm. on the sixtieth day; 30 mm. on the seventy-fourth day. The sedimentation rate was still rapid on the eighty-fourth day and the man was transferred to another activity.

Comment: This man had a gonococcal arthritis, as evidenced by history of previous attack, failure of the joints to react to salicylates and the residual thickening of the involved articulations. The electrocardiogram gave evidence of myocardial damage.

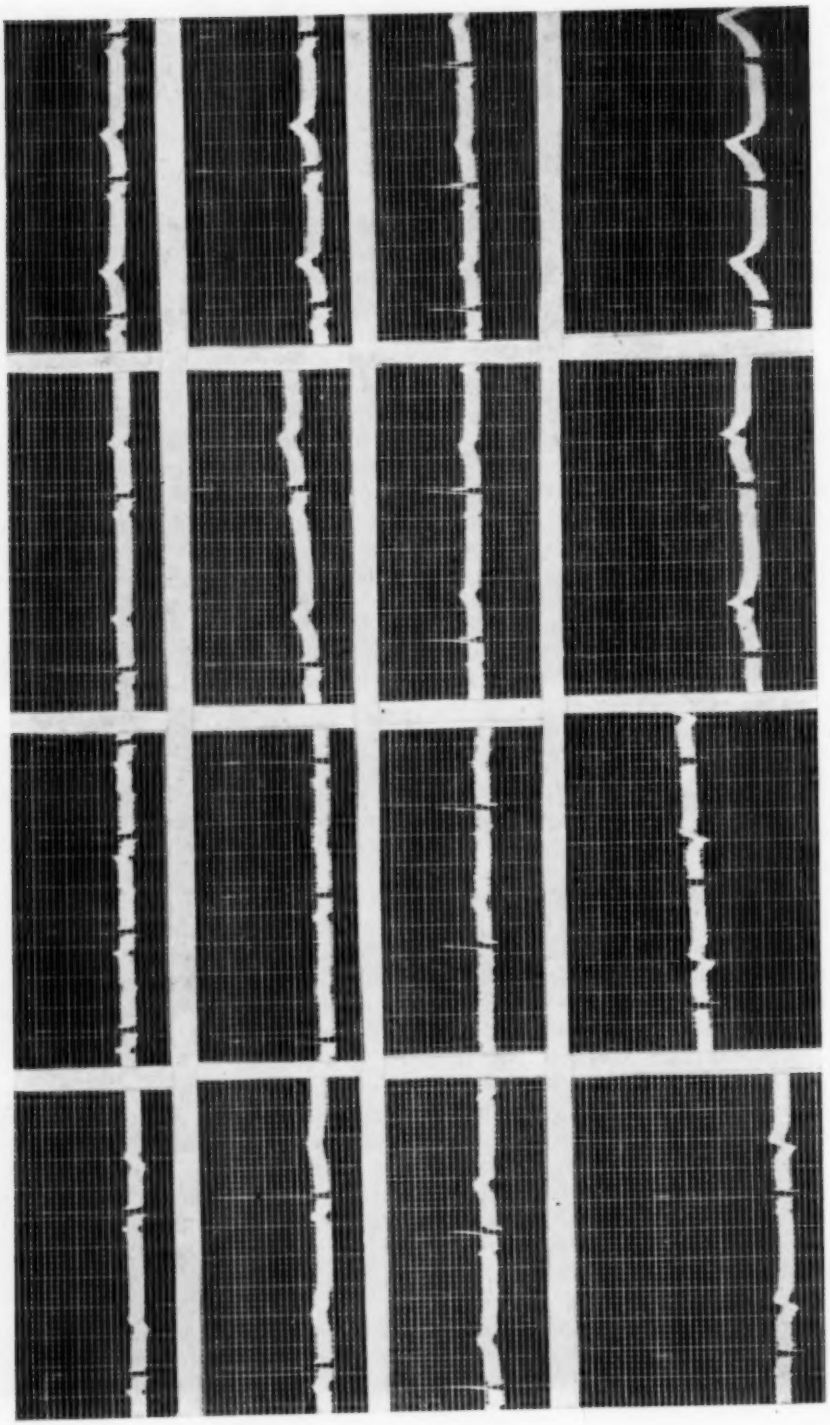


FIG. 4. *Case 4.* Diagnosis: Scarlet fever; acute, non-specific myocarditis. T-wave inversion in Leads I and IV; T_1, T_2 changes in L_1 and L_2. Normal tracing on the fifty-seventh day.

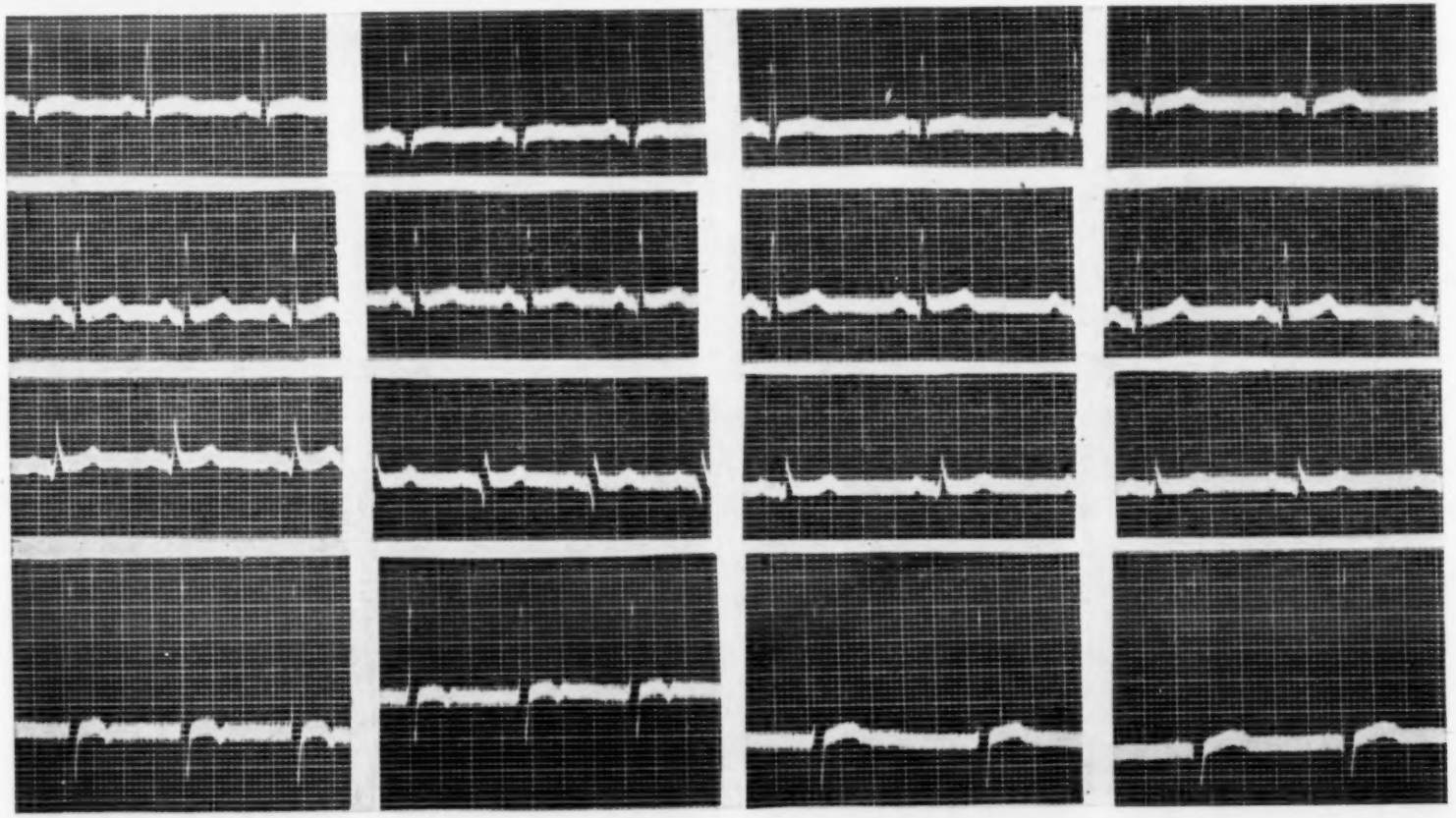


FIG. 5. *Case 5.* Diagnosis: Acute recurrent gonococcal arthritis; acute non-specific myocarditis. T-wave changes in L_1 and L_2. Normal tracing on sixty-fourth day.

Case 6. Diagnosis: Acute gonococcal arthritis; acute non-specific myocarditis.

R. L. B., S2c, aged 19 years, was treated for a specific urethritis on March 11, 1943. After a course of sulfathiazole the urethral discharge ceased. On March 20 he had a recurrence of his urethral discharge. This was associated with swelling of the right great toe and right knee. On admission, March 21, both knees were swollen. Temperature was 101° F. The temperature was elevated daily up to at least 100° F. for two months. Both ankles became swollen. The right sternoclavicular joint likewise was involved. The arthritis was non-migratory. When the process subsided, the joints were left with periarticular thickening. On April 3, 100 c.c. of a cloudy, straw-colored fluid were aspirated from the right knee. Gram negative diplococci were demonstrated in the fluid. The arthritic process was refractory to a full course of sulfathiazole and to massive doses of salicylates. The erythrocyte sedimentation rate, rapid on admission, was still 30 mm. in one hour at the end of two months. There was no evidence clinically of cardiac abnormality. Roentgenogram of the heart showed it to be normal in size and shape. An electrocardiogram done on the twelfth day after the onset of arthritis was within normal limits (figure 6). On the twenty-sixth day T_1 was low, T_2 diphasic, T_4 became inverted. On the sixty-sixth day T_1 had become more positive. On the ninetieth day T_4 was again upright and the electrocardiogram more nearly approached the normal.

Comment: A case of gonococcal arthritis showed electrocardiographic evidence of myocarditis over a period of three months.

Case 7. Diagnosis: Acute gonococcal arthritis; acute non-specific myocarditis.

S. S., S2c, aged 37 years, was treated on February 12, 1944 for gonococcal urethritis. One week later he developed swelling of the right knee. He was admitted to the sick bay. Both knees, both ankles and the right large toe became involved. The arthritis was non-migratory and was not affected by salicylates or sulfadiazine. On March 21, a course of penicillin for one day resulted in prompt subsidence of urethral discharge. The erythrocyte sedimentation rate was 27 mm. on admission and became normal on the eighty-seventh day. He was returned to duty three and one-half months after admission. On February 19, the day of onset of arthritis, an electrocardiogram was normal (figure 7). On February 23 T_1 was biphasic; T_2, T_3 and T_4 were inverted. T_4 became upright on the twelfth day after onset of arthritis. T_1 became positive but remained low on the fourteenth day. On the fifty-first day T_1 and T_2 were still low.

Comment: A case of acute gonococcal arthritis was complicated by acute myocarditis as shown by the changes in the electrocardiogram.

Case 8. Diagnosis: Stricture, urethral; urinary retention; cystitis, acute; acute non-specific myocarditis.

S. P., GM2c, colored, aged 35 years, gave a history of difficulty in urination since an episode of gonorrheal urethritis in 1941. After he had been on leave for two days, he had increasing difficulty on urination. He developed urinary retention. When he could not be relieved by his local doctor, he returned to this activity. It was impossible for the urologist to pass a catheter or filiform bougie. A suprapubic cystotomy was done on January 4, 1944. The urine was loaded with pus cells. On January 27, 1944 the perineum was opened and a catheter inserted through the urethra into the bladder. At a later date, when the urethral catheter was removed, the patient was unable to urinate. The suprapubic wound was reopened, blood clots were removed, and a urethral catheter reinserted via the urethral orifice in the bladder. The patient made good progress postoperatively.

Two days after the last procedure, the man developed a tachycardia and consultation was requested. On February 10 the pulse was 120, blood pressure 150 mm. Hg systolic and 90 mm. diastolic, temperature 100° F. Physical examination was negative except for the cystotomy wound. Roentgenogram of the heart was normal

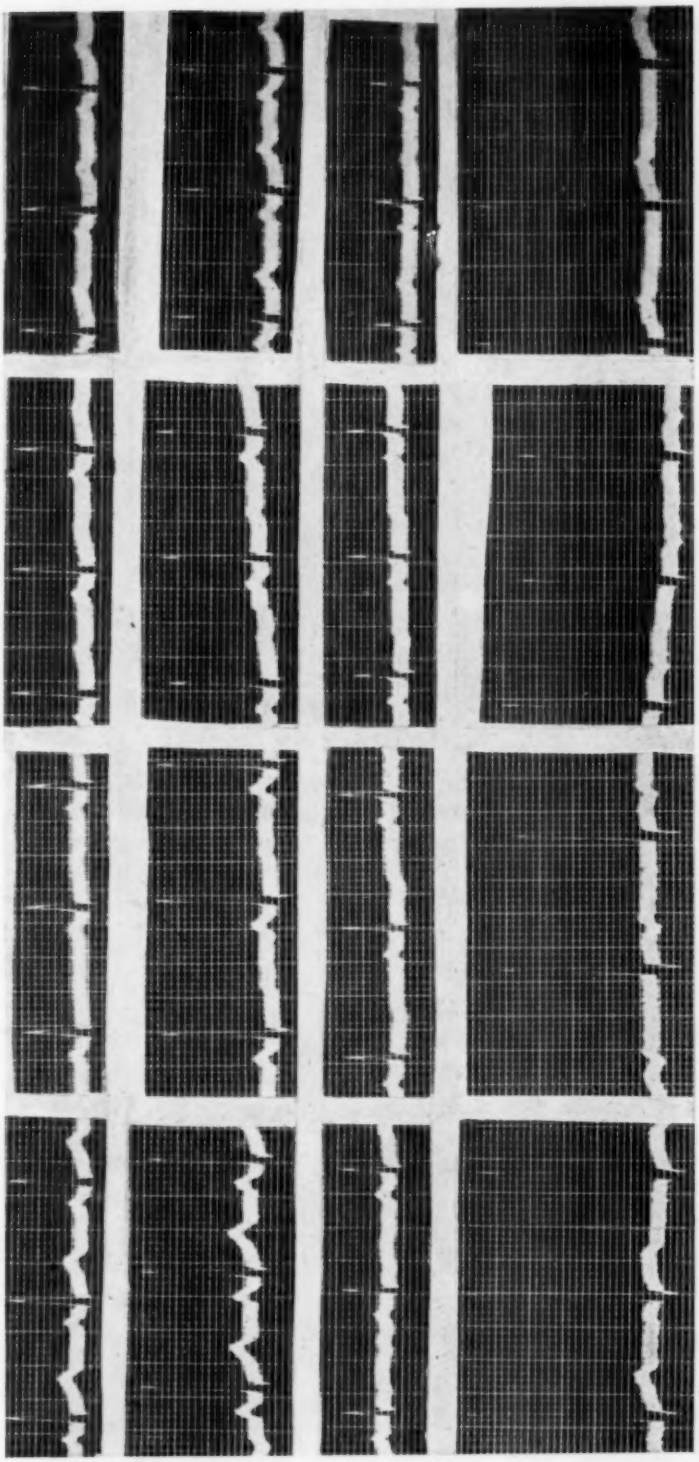


FIG. 6. *Case 6.* Diagnosis: Acute gonococcal arthritis; acute non-specific myocarditis. T-wave changes in L_1, L_2, L_3, L_4; normal tracing on nintieth day.

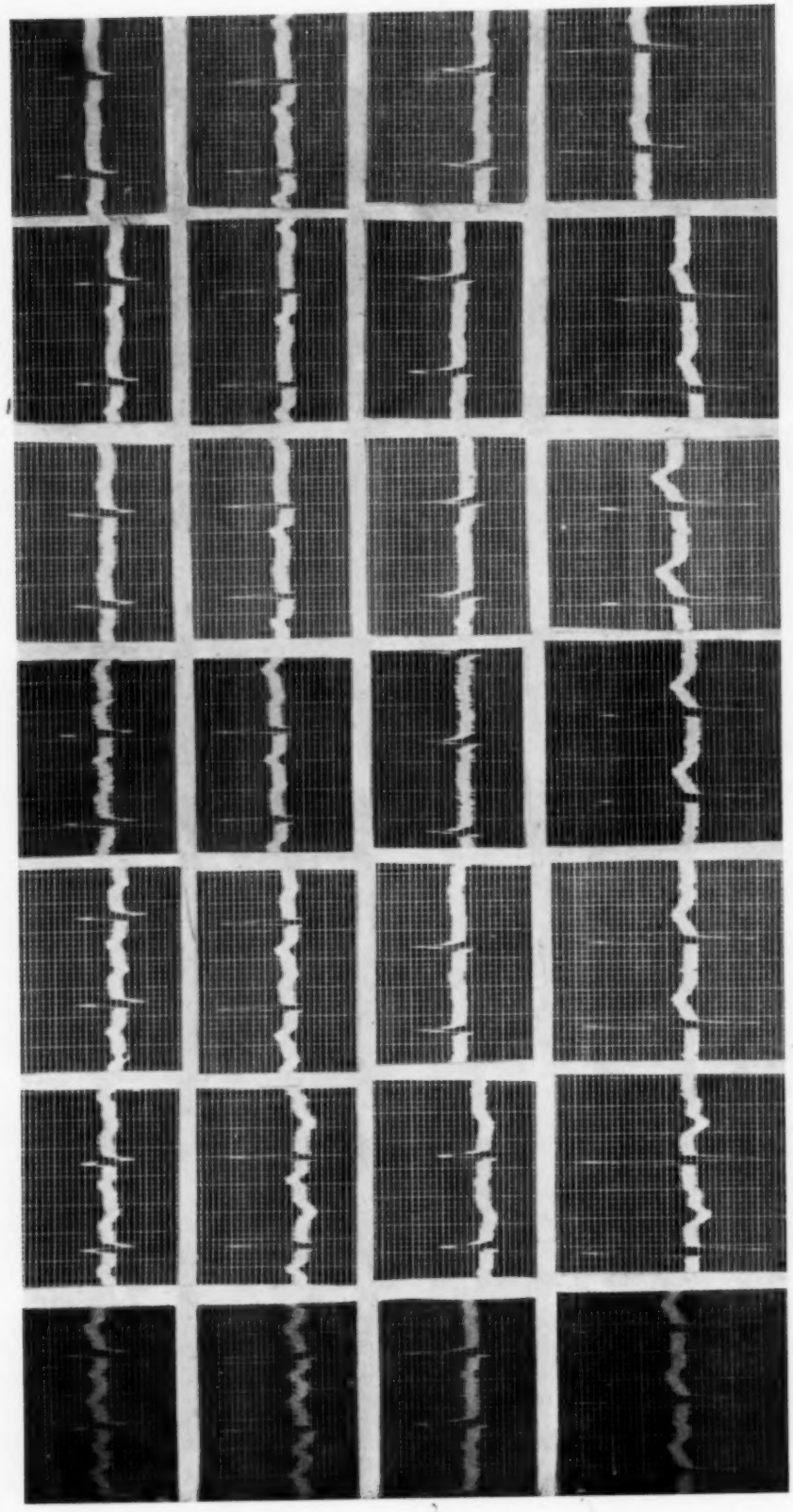


FIG. 7. *Case 7.* Diagnosis: Acute gonococcal arthritis; acute non-specific myocarditis. T-wave changes on the fourth day; T_1 and T_2 still low on fifty-first day.

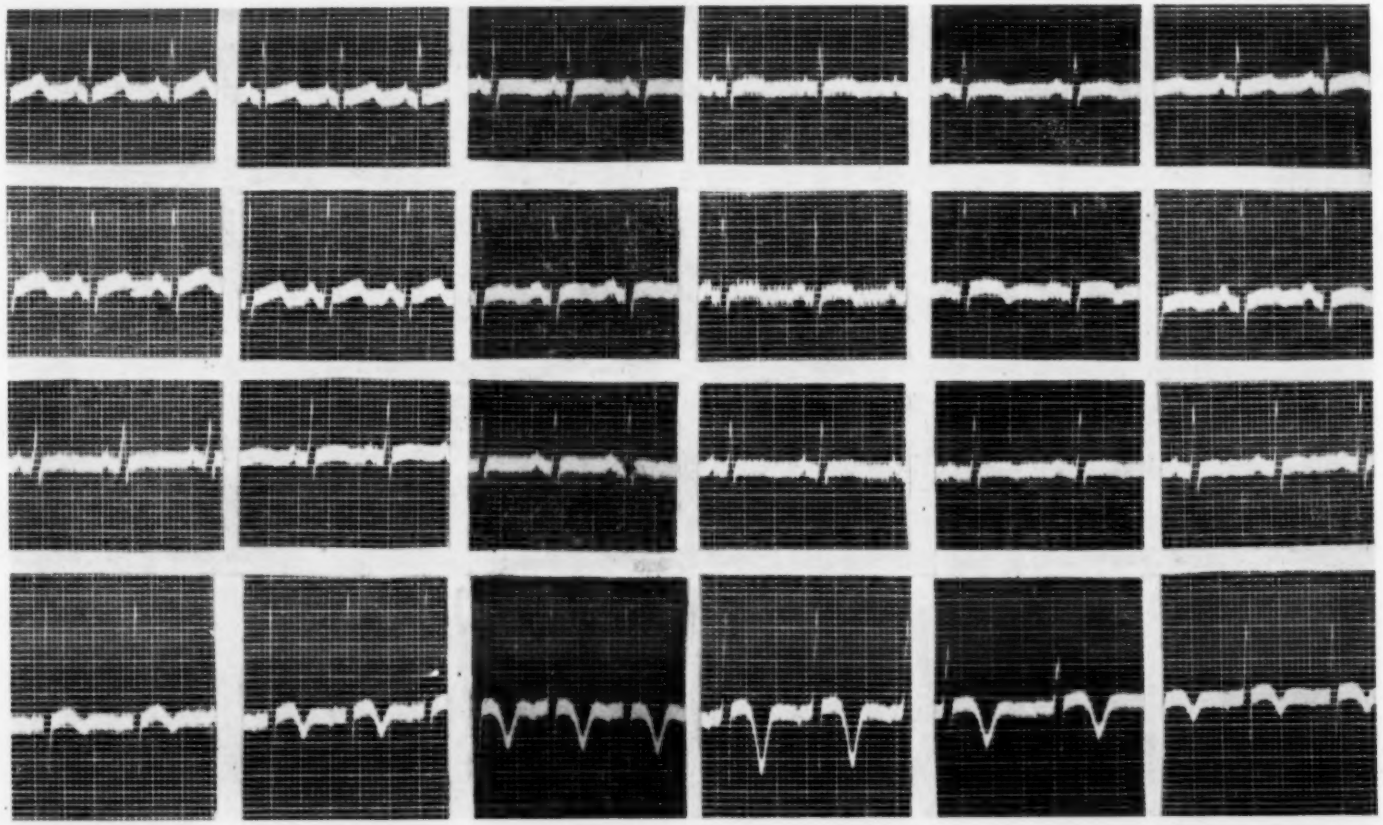


FIG. 8. *Case 8.* Diagnosis: Stricture, urethral; cystitis, acute; acute non-specific myocarditis. First electrocardiogram taken on first post-operative day following the last procedure, i.e. 37 days after original admission. T-wave changes in L_1, L_2, and L_4.

as to size and shape. An electrocardiogram done on February 10 showed a sinus tachycardia with a biphasic T_4 (figure 8). Another tracing four days later showed a marked inversion of T_4. On the thirteenth day after the first tracing, T_1 was isoelectric, T_2 was low, and T_4 was sharply inverted. On the twenty-third day T_1 was biphasic, T_2 inverted, T_4 a little less inverted. On the twenty-ninth day T_1 was upright, T_2 was upright, T_4 was becoming less negative.

Comment: This was a case of acute cystitis, with a tachycardia and electrocardiographic evidence indicative of an acute myocarditis.

Case 9. Diagnosis: Infectious mononucleosis; acute non-specific myocarditis.

R. H. C., Lt.(jg), aged 24 years, had a sore throat on May 2, 1944. His temperature on admission was 100.2° F. The erythrocyte sedimentation rate was 5 mm. in one hour. For the first two weeks the temperature was low grade and did not exceed 100° F. Blood counts were reported as normal. On May 16 a blood count showed 4,900 cells with 62 polymorphonuclear cells, 35 lymphocytes and 3 monocytes. On May 18 the spleen was palpable and the right submaxillary nodes were swollen and tender. On May 22 the erythrocyte sedimentation rate was 18 mm. in one hour. He developed a generalized lymphadenopathy. On May 24 a blood count showed 11,400 cells with 31 per cent polymorphonuclear leukocytes and 69 per cent lymphocytes. Many of the lymphocytes were atypical and characteristic of infectious mononucleosis. A heterophile agglutination test was positive in a dilution of 1–2560. From May 14 to May 28 he ran a stormy febrile course with elevations reaching 103° F. daily. During the next two weeks he showed a low grade temperature, which became normal. Serial electrocardiograms showed a biphasic T_4 on the seventeenth day (figure 9). On the twenty-second day T_4 was upright, T_3 isoelectric, T_2 a little low. T_4 changes were again noted on the twenty-fourth and thirty-first days.

Comment: The electrocardiographic alterations were indicative of myocarditis in the course of a case of infectious mononucleosis.

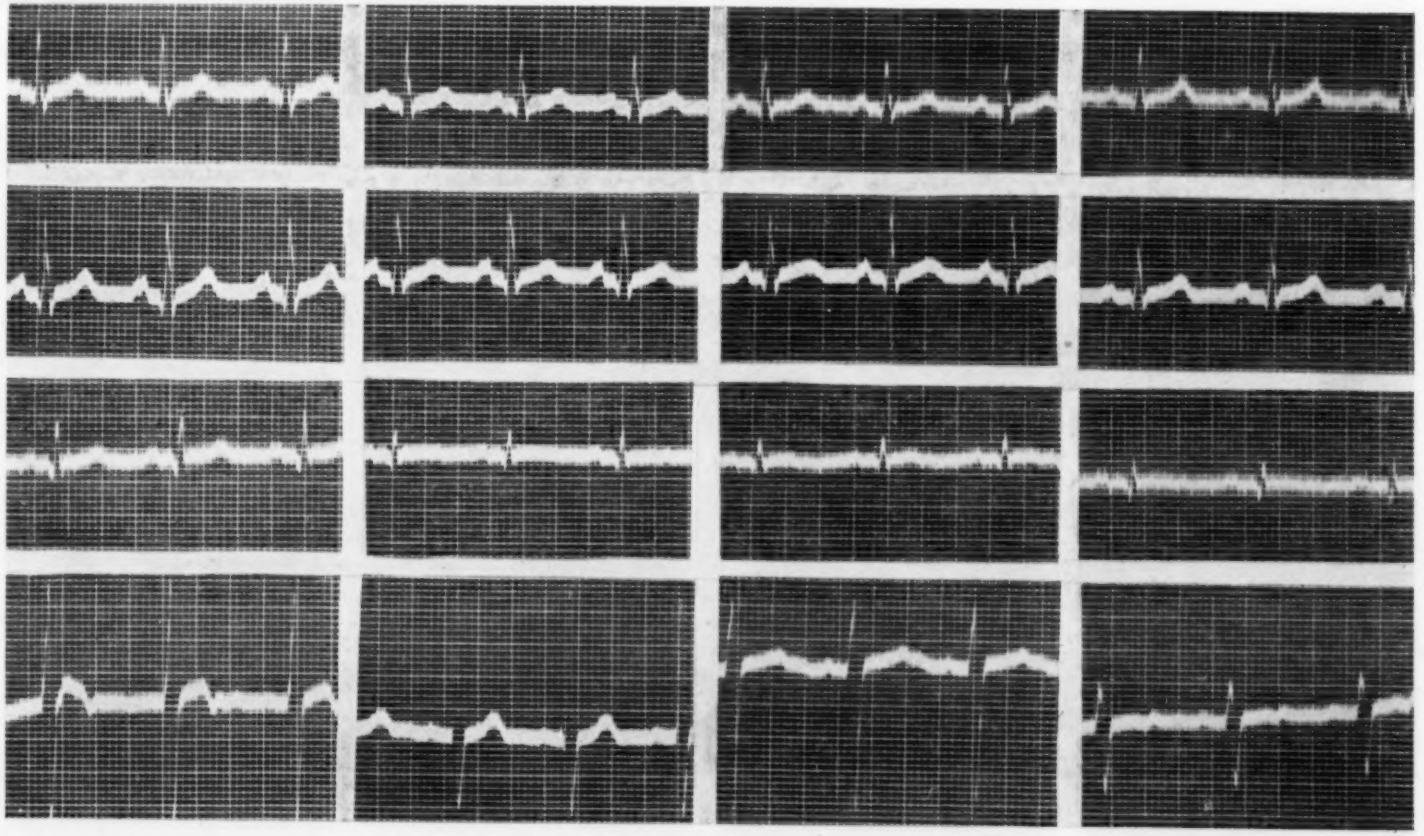
Case 10. Diagnosis: Typhus fever; acute non-specific myocarditis.

S. P., S1c, aged 23 years, was admitted on April 24, 1944 with a sore throat, chills, fever and headache. On April 28 he developed a fine macular eruption. On April 28 the Weil-Felix reaction was positive in dilution of 1–80 and on May 9 the Weil-Felix reaction was positive in dilution of 1–320. He became afebrile on the eleventh day. The erythrocyte sedimentation rate was 16 mm. on the fifth day and 19 mm. on the twentieth day. It was normal on the forty-ninth day. An electrocardiogram on the ninth day showed a P–R interval of 0.28 second. On the fifteenth day it was 0.30 second; on the twenty-sixth day, 0.24 second; on the thirty-seventh day, 0.20 second. It was still 0.20 second on the seventy-ninth day (figure 10).

Comment: The varying abnormal P–R intervals were indicative of an acute myocarditis.

Case 11. Diagnosis: Typhus fever; acute non-specific myocarditis.

A. H., M2c, aged 29, was admitted on October 30, 1944 with the complaint of fever, malaise, headache and dry cough for three days. Physical examination was negative except for slight nuchal rigidity. A spinal tap was done and no cells were found in the fluid. A white blood cell count showed 6,400 cells with 71 per cent polymorphonuclear leukocytes, 27 per cent lymphocytes, 1 per cent basophiles, and 1 per cent monocytes. The urine examination was within normal limits except for a 1-plus albumin. The erythrocyte sedimentation rate was 20 mm. in one hour (Cutler method). He developed marked cerebral symptoms, and numerous crepitant râles were heard throughout the chest. A fine macular eruption appeared on the sixth day of disease (three days after admission). He ran a severe febrile course through the twelfth day, after which there was a rapid lysis by the fourteenth day. On the sixteenth day the temperature was 99° F. A Weil-Felix reaction showed no agglutination on the sixth day of disease. It showed a positive agglutination on the seventh, tenth, and twelfth days in dilutions of 1–40, 1–60, and 1–640 respectively.



17th Day 22nd Day 24th Day 31st Day

FIG. 9. *Case 9.* Diagnosis: Infectious mononucleosis; acute non-specific myocarditis. T-wave changes in L_4.

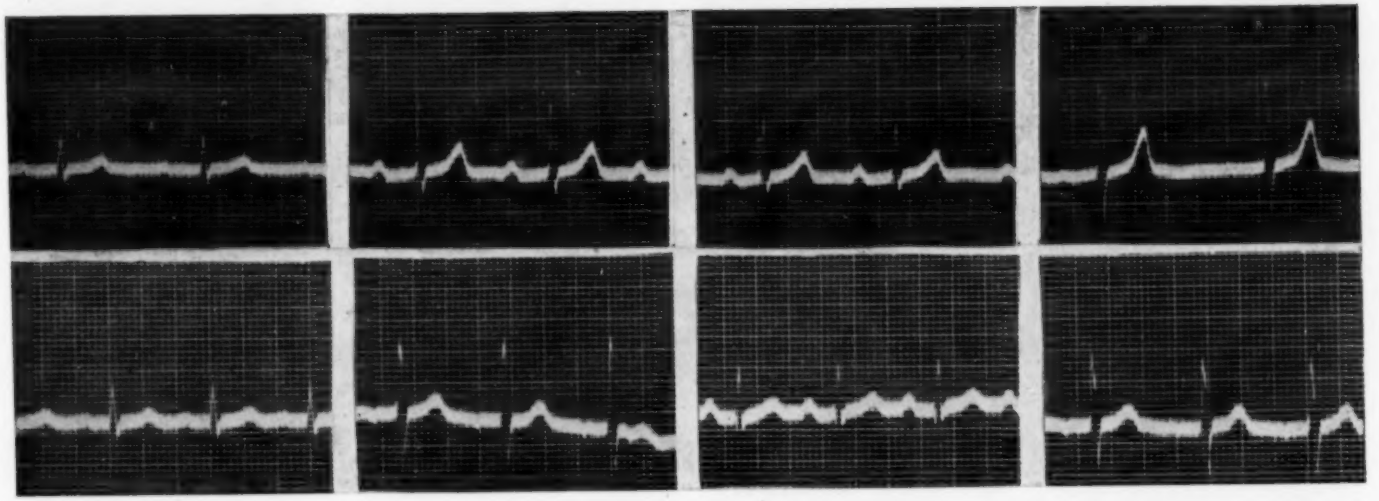


FIG. 10. *Case 10.* Diagnosis: Typhus fever; acute non-specific myocarditis. P–R interval prolonged. Electrocardiograms showed P–R intervals of 0.28 second on the ninth day; 0.30 second on the fifteenth day; 0.24 second on twenty-fifth day; 0.20 second on the thirty-sixth day; 0.20 second on seventy-ninth day. Only tracings on fifteenth and seventy-ninth days are reproduced.

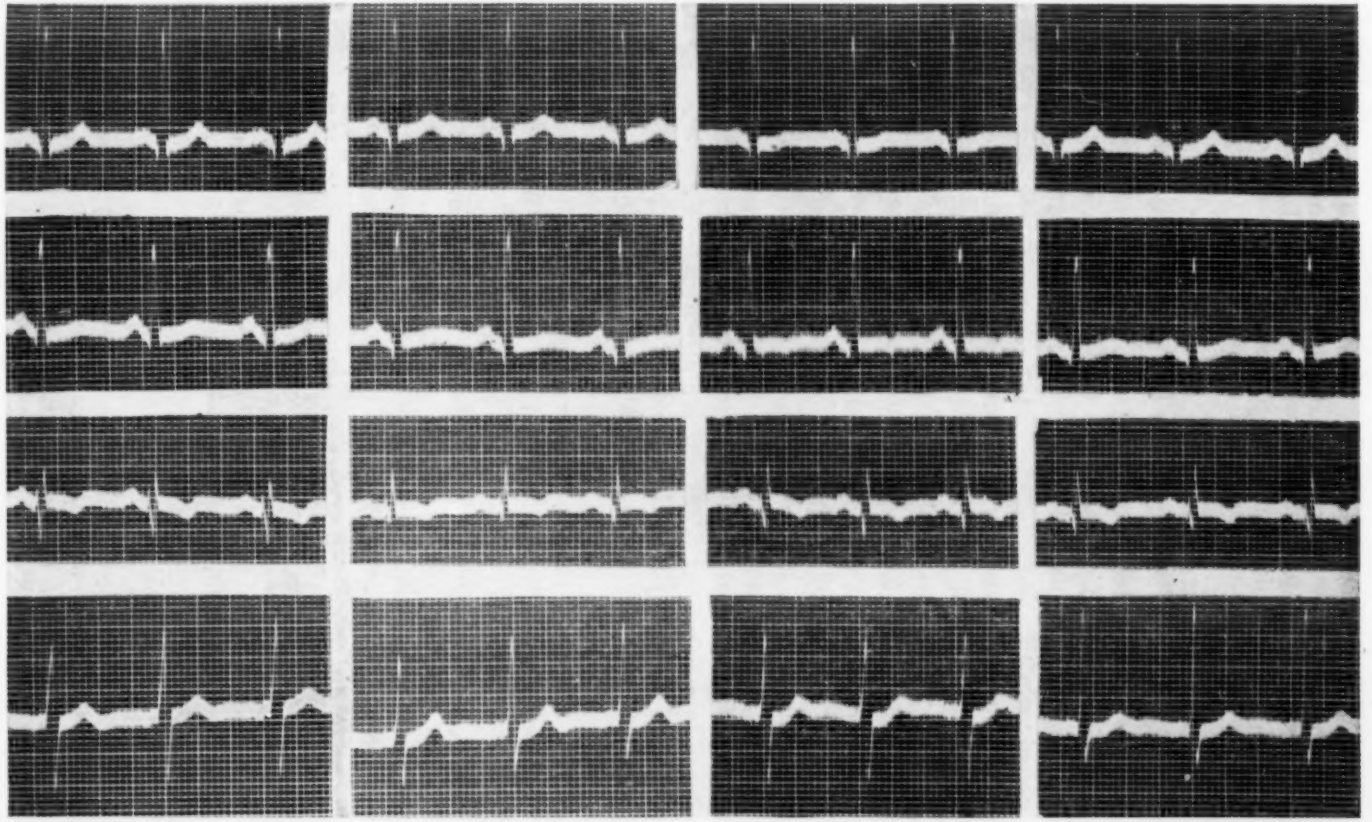


FIG. 11. *Case 11.* Diagnosis: Typhus fever; acute non-specific myocarditis. T_2 low on the fourth day. T_1 low and biphasic and T_2 inverted on the fifteenth day. T_1 upright and T_2 upright although still low on the nineteenth day.

An electrocardiogram done on the fourth day of disease (second day after admission) showed a left axis deviation and a low T_2. The electrocardiogram was repeated every three days. There was no variation until the twelfth day when T_2 was a little flatter. On the fifteenth day T_1 was biphasic and T_2 inverted. On the nineteenth day T_1 had returned to normal and T_2 became upright but was still low.

Comment: A case of typhus fever showed electrocardiographic evidence of acute myocarditis as shown by T-wave changes in L_1 and L_2 of the electrocardiogram.

The 11 cases just presented had the following characteristics in common:

(*a*) Each was associated with an acute infectious disease with the additions that case 3 was seen two weeks after discharge from treatment for pneumonia and case 5 had an acute recurrence of a gonococcal arthritis.

(*b*) Each showed significant electrocardiographic alterations.

(*c*) Each had a rapid erythrocyte sedimentation rate even when the primary disease had apparently abated (with the exception of case 8, where no erythrocyte sedimentation rate was done).

Attention was drawn to the possibility of acute myocarditis in case 2 because of extrasystoles and a gallop rhythm, in case 8 because of a persistent tachycardia without fever, in case 3 because of the symptom of breathlessness. Attention was focused on the electrocardiogram in cases 4, 5, 6 and 7 because most observers are conditioned to look for evidence of myocarditis in any disease in which joint symptoms are prominent. Cases 1, 9, 10 and 11 were studied because of marked toxemia and our curiosity to see if there were any evidences of myocardial involvement by the underlying disease.

We did not attempt to carry on any investigation of all the patients with acute infections or severe toxemia who came under our observation. We can make no statement, therefore, as to the frequency of occurrence of acute myocarditis. These 11 cases merely represent 11 observations collected during the past months.

Case 1 in our series was one of acute myocarditis, secondary to a peritonsillar abscess. Scherf [13] published five cases of acute myocarditis following tonsillar infection. One of these followed a peritonsillar abscess. In Scherf's experience, 10 to 15 per cent of patients with acute tonsillitis develop symptoms, signs or electrocardiographic changes which suggest myocardial involvement. He found that the occurrence of myocarditis apparently had no relationship to the severity of the tonsillitis. He quoted Hotz and Huber; and Otto, who reported an incidence of myocarditis of 63 per cent and 67 per cent in their series of tonsillitis. However, Scherf stated that these authors included patients with minor changes of the electrocardiogram which might well have been normal variations. Maher and Wosika [12] have recorded a case of a patient with peritonsillar abscess and electrocardiographic evidence of myocarditis. Other authors have observed similar phenomena in the course of acute tonsillitis.[14] Saphir,[1] in summarizing myocarditis associated with tonsillitis, wrote: "one notes that little

concrete evidence and practically no observation at autopsies are available to answer the question whether myocardial changes occur as a result of tonsillar infections. There are students who believe that fleeting electrocardiographic changes signify anatomic lesions, whatever they may be. There are others, more cautious, who do not accept the statements as to myocarditis in these without more anatomic proof than is available today. . . ."

We wish to record a case of acute suppurative tonsillitis followed by sudden death due to acute non-specific myocarditis. This patient was seen by neither of us clinically, but was autopsied by one of us at another institution.

F. D., male, aged 24, was admitted to the hospital on December 30, 1943. He appeared moderately ill and stated that his illness began two days previously with headache, malaise, congested nose, sore throat and fever. Physical examination was negative except for a moderately injected pharynx, congested nasal mucosa, and a temperature of 101° F. The following day, December 31, he appeared comfortable and had a temperature of 102° F. Physical examination showed an increased redness of the pharynx. His tonsils appeared moderately swollen and red. He was given sulfathiazole, one gram every four hours. On January 1, 1944, his temperature was 99° F. He felt better. His tonsils were less swollen. He sat up in bed, conversed with patients around him. He was seen to go to the head. On January 2, 1944 he awoke at 0010 and spoke to an attendant. He made no complaint and appeared well. At 0600 he was found dead in bed.

An autopsy, including examination of the brain, was done. The most significant findings described in the protocol are summarized:

Cultures from the throat and nasopharynx showed the *Streptococcus hemolyticus beta*.

In the pharynx there was marked hyperplasia of the faucial and lingual tonsils with prominent crypts which were filled with thick purulent exudate. A similar exudate was present in the nasopharynx.

The heart weighed 387 grams. The right ventricle was 2 mm. in thickness and the left ventricle was 15 mm. in thickness. The valve measurements in circumference were as follows: tricuspid, 13 cm.; pulmonary, 5 cm.; aortic, 5.2 cm.; mitral, 9 cm. The heart on inspection was increased in size owing to dilatation of the right ventricle. This was substantiated by the measurements as given above. The epicardium was smooth, glistening and transparent. There was some fat deposited over the right ventricle. In addition, there were small ecchymoses beneath the epicardium along the atrioventricular sulci. The heart muscle was soft, reddish-brown, and contained yellow and gray streaks running through it. The valve leaflets were soft and pliable and there were no adhesions. The endocardium was smooth throughout, except in the left atrium where there were some small linear streaks of fibrous thickening. Sections through the interventricular septum showed the changes in the myocardium already described. The coronary arteries were patent throughout. There was a yellow deposit in the intima of right and left coronary arteries. The aorta was elastic and contained yellow deposits similar to those present in the coronary vessels.

Microscopic Examination. Heart wall, left ventricle: The epicardium showed a thin layer of fibrin on the surface and an infiltration of polynuclear cells. There was very little fat present. In the myocardium there was pronounced fragmentation of the bundles with the loss of the usual cross striations. In addition, there was a widespread diffuse infiltration of the interstitial tissue by polynuclear cells. There was a very slight tendency for the inflammatory reaction to be perivascular. No Aschoff nodules or cells were present. The endocardium was focally thickened over

the papillary muscles and contained scattered polynuclear cells in its underlying tissue. A second section of heart wall from the left ventricle showed those changes already described, but of a more widespread character (figures 12 and 13).

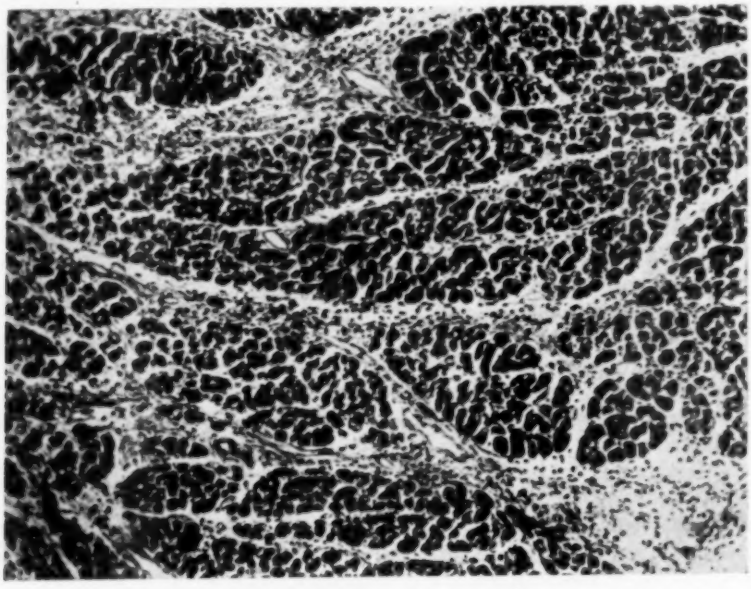


FIG. 12. Acute non-specific myocarditis following acute suppurative tonsillitis. Low Power: Diffuse infiltration of myocardium by polymorphonuclear leukocytes.

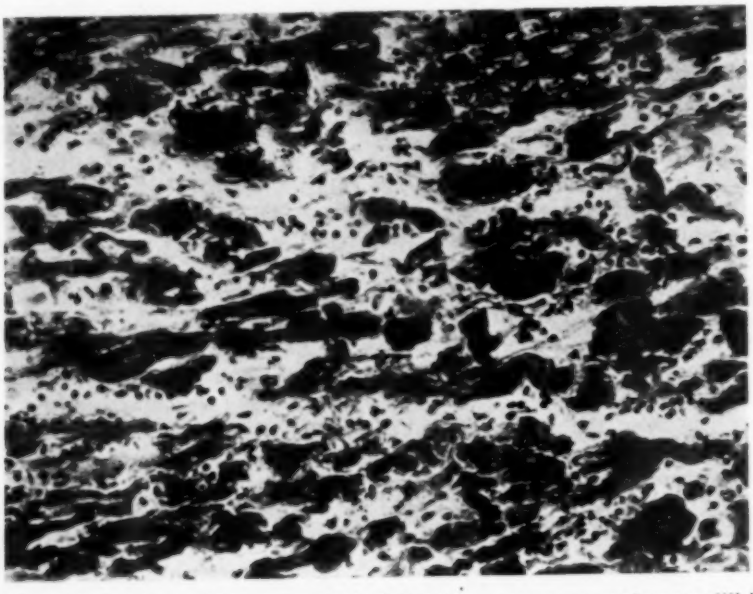


FIG. 13. Acute non-specific myocarditis following acute suppurative tonsillitis. High Power: Fragmentation of muscle bundles; loss of cross striations; disintegration of muscle nuclei; edema of interstitial tissue; infiltration of polymorphonuclear leukocytes.

Atrium: There was a slight thickening of the endothelium.

Pulmonary artery: Normal.

Heart wall: Right ventricle showed a minimal amount of fat infiltration. The acute inflammatory change in the interstitial tissue was not so marked on this side as it was on the left.

Aorta: Showed early lipoid deposits in the subintimal tissue.

Coronary artery: Showed slight change in the intima with endothelial and fibroblastic proliferation and some lipoid deposits.

Pharyngeal and Faucial tonsils: Showed marked hyperplasia of the lymphoid tissue, accumulation of exudate in the crypts, and infiltration in the epithelium which consisted of polynuclear cells, plasma cells, and eosinophiles.

Lingual tonsil: The lingual tonsils were similar to but less extensively involved than the pharyngeal tonsil.

Anatomic Diagnosis. 1. Acute suppurative nasopharyngitis and tonsillitis. 2. Acute diffuse myocarditis. 3. Parenchymatous degeneration of liver and kidneys. 4. Passive hyperemia of lungs, liver, kidneys. 5. Acute hyperplasia of spleen and lymphoid follicles of colon, ileum; cervical, mediastinal, pancreatic and mesenteric lymph nodes. 6. Hypertrophy of heart—slight. 7. Primary tuberculous focus, upper lobe of left lung, obsolete. Fibrous pleural and peritoneal adhesions. Remote appendectomy. Persistent thymus.

It is unfortunate that no electrocardiograms were obtained from the patient just described. The clinician had observed a man with acute tonsillitis who, in vivo, presented no sign or symptom pointing towards a cardiac disorder. This one case has great significance. It demonstrates that acute myocarditis may follow acute tonsillitis. Since much electrocardiographic evidence has been collected to show that myocardial disturbances are not at all rare in acute tonsillitis, it is not unsafe to assume that these electrocardiographic alterations actually are due to an acute myocarditis. Sudden death or cardiac decompensation following tonsillitis is rare. It is reasonable, then, to assume that the vast majority of the cases of acute myocarditis following tonsillitis recover completely. This is borne out by the observations of the electrocardiographic changes which show that they most often return to normal. A few may heal and retain permanent evidence of a previous myocarditis as shown by some permanent abnormal electrocardiographic alteration.

Saphir [15] found acute myocarditis in 19 cases of bronchopneumonia and seven cases of lobar pneumonia. Stone, quoted by Fishberg,[16] observed parenchymatous, fatty or hyaline degeneration or cellular infiltration in 79.3 per cent of his necropsies. Fishberg points out that Master, Romanoff and Jaffe detected electrocardiographic changes in over 93 per cent of 45 patients with lobar pneumonia and that De Graff, Travell, and Yager, taking less frequent records, found electrocardiographic abnormalities in about one quarter of 975 cases. The changes, almost always transitory, included prolongation of the P–R interval, abnormalities of the RT transition; flat, inverted and large T waves; intraventricular block. Master and his associates demonstrated changes in the R–T interval that apparently simulated those seen in coronary disease. In 78 per cent of the cases it was shown that the

electrocardiographic changes appeared after the temperature dropped to normal.

In our series, case 3 (acute myocarditis following a primary atypical pneumonia) showed a complete A–V dissociation; then a normal rhythm with a prolonged P–R interval; and finally a normal tracing. Case 2 (acute myocarditis associated with lobar pneumonia) showed a bundle branch block which persisted for 96 days and was still present when the man was transferred.

Saphir,[17] in his article on Myocarditis in Bronchiectasis, quotes Brody and Smith who found myocardial involvement in 90 per cent of 44 hearts of patients dying from scarlet fever. Case 4 demonstrates electrocardiographic alterations in a patient with scarlet fever myocarditis.

Isolated involvement of the myocardium in gonococcic infection is rare, according to Saphir. The lesions are, for the most part, foci of acute myocarditis and foci of necrosis. The inflammatory process is thought to occur as the result of direct extension into the myocardium from endocardial or valvular lesions. Bang [18] reported six cases of gonorrheal myocarditis diagnosed by electrocardiographic alterations in the course of the disease. Five cases were associated with acute recurrent gonococcal arthritis. One case was an acute gonococcal arthritis following an acute specific urethritis. Bang quotes Dittrick, who reported two instances of isolated myocarditis complicating gonococcal arthritis, showing tachycardia and arrhythmia. Bang also collected a case reported by Guldberg in 1935. He found no other references in the literature. Logue and Hanson [19] found eight cases of heart block among 530 cases of sulfonamide-resistant gonorrhea. They stated that the cause of heart block in this group is not clear. It is likely that they were instances of myocarditis. Of the three cases of gonococcal myocarditis which we observed, Case 5 was associated with a recurrent gonococcal arthritis whereas cases 6 and 7 were associated with a first attack.

Infection of the urinary tract may be the cause of an acute myocarditis. Saphir found four such instances in his study. Case 8 illustrates an acute myocarditis, secondary to a urinary tract infection as evidenced clinically by a tachycardia, and electrocardiographically by tracings showing myocardial damage.

We encountered one case of infectious mononucleosis (case 9) with evidence of myocarditis. Logue and Hanson found in their study one case of infectious mononucleosis with first degree heart block.

Herzog and Rodriguez, according to Saphir,[15] examined 103 hearts of patients who died of typhus fever and found evidence of myocarditis in 97 per cent of their cases. Most of the microscopic changes were focal. Cases 10 and 11 in our series had typhus fever. Case 10 showed evidence of acute myocarditis by a prolonged A–V conduction time that varied during the course of the disease, whereas case 11 showed T-wave changes which varied in Leads I and II.

Acute myocarditis occurs secondary to many diseases of bacterial or virus origin and to some conditions of undetermined etiology. The myocardial lesions may result either from direct invasion of the heart by the offending organism or from toxins circulating through the blood stream. The following incomplete list mentions some of the conditions in which acute myocarditis has been demonstrated at autopsy: rheumatic fever, diphtheria, typhoid fever, paratyphoid fever, typhus fever, dysentery, mumps, pneumonia, scarlet fever, meningococcus infection, gonococcic infection, tularemia, acute bacterial endocarditis, streptococcic and pneumococcic meningitis, tuberculosis, pyelitis, acute glomerular nephritis, pyemia, subacute bacterial endocarditis (Saphir [15]); purulent otitis media, conjunctivitis and stomatitis (Maslow and Lederer [2]); pyodermia (Maxwell and Barrett [3]); bronchiectasis (Saphir [17]); acute suppurative tonsillitis (authors' case).

A special form of myocarditis has been recorded in the literature under the terms idiopathic myocarditis, Fiedler's myocarditis; isolated myocarditis, interstitial myocarditis, acute or subacute productive myocarditis, fibrous myocarditis. Under the microscope it cannot be differentiated from other types of acute non-specific myocarditis. The diagnosis is usually made after autopsy. This group of myocarditis has the distinction of being classified separately because no evidence of a primary disease is demonstrable at autopsy. This is far from saying that there was no primary infectious agent.

According to Karsner,[20] the differentiation between acute parenchymatous and acute interstitial myocarditis does not seem justifiable. An acute myocarditis may become subacute or chronic, based arbitrarily on duration. Englehardt and Bruno [8] recorded a case of Fiedler's myocarditis in which decompensation occurred over a period of 21 months. Smith and Stephens [19] observed cases of decompensation due to interstitial myocarditis whose clinical course ran several months to two years. Several classifications of myocarditis have been offered on the basis of pathology. Saphir [1] has presented his own classification and discussed those of Brown and Hunt, of Vischer, and of Marshall. We prefer the classification of Marshall, with the modification that isolated myocarditis be grouped not as a specific entity, but as a sub-group of non-specific myocarditis. A modified classification of infectious myocarditis may be stated as follows:

INFECTIOUS MYOCARDITIS

1. Specific myocarditis.....(Rheumatic, tuberculous, syphilitic)
2. Non-specific myocarditis....(*a*) Known etiology —(Diphtheria, tonsillitis, typhus fever, bronchiectasis, etc. or clinical entity of undetermined etiology such as infectious mononucleosis)

(*b*) Unknown etiology—Fiedler's myocarditis

(3) Septic myocarditis.....in septicemia and in association with subacute bacterial endocarditis.

Fetal myocarditis is included by Saphir as a separate group, but with some question as to its occurrence. Only a few references appear on this con-

dition in the older literature in connection with observations on congenital heart disease, in which intra-uterine cardiac inflammation was suspected as the underlying factor.

The classification of acute myocarditis from a clinical standpoint is difficult. In a general way we may find the following groups which show:

1. Signs
2. Symptoms
3. Signs and symptoms
4. Neither signs nor symptoms.

The signs and symptoms of acute myocarditis have been well discussed elsewhere.[11, 21] Angina pectoris, palpitation, breathlessness, asthenia, arrhythmia, and gallop rhythm following acute infection have been noted. Left or right ventricular failure, or both, may occur as a result of myocardial insufficiency.

The criteria for diagnosis of acute myocarditis as set down in the publication of the New York Heart Association [22] may be followed. The diagnosis can be made correctly more often than it is. The first requisite for recognition of the condition is the appreciation that acute myocarditis is not a rare complication of infectious disease, acute or chronic. Patients, whose convalescence from acute infection is slow and who complain of profound asthenia after the acute disease has apparently subsided, should be examined carefully for evidence of myocarditis. The symptoms of slight precordial discomfort, angina pectoris, or breathlessness associated with or occurring shortly after the termination of an acute infectious disease, should be regarded with suspicion. Arrhythmias and gallop rhythm should be thoroughly investigated. A persistently rapid sedimentation rate after the primary infectious disease process has subsided should likewise make the physician study his patient carefully for a possible complicating myocarditis.

There is a group of patients who develop myocarditis after an infectious disease and show no arrhythmias, no symptoms referable to the heart and in whom the electrocardiogram may or may not reveal evidence of myocardial disease. Scherf and Boyd [11] have pointed out that alterations of the electrocardiogram are not evident in every case nor continually in the positive ones. It is to this group that more attention should be directed. Until our present knowledge of physical diagnosis is more advanced, or perhaps more wisely utilized, the diagnosis of myocarditis in these individuals will rest mainly with the demonstration of myocardial involvement by means of the electrocardiogram and often by repeated electrocardiograms.

The significance of electrocardiographic abnormalities in the diagnosis of acute non-specific myocarditis is not fully recognized. This is indeed strange. In the course of acute rheumatic fever, electrocardiographic alterations such as profound arrhythmias and T-wave changes are accepted as unequivocal evidence of disease of the myocardium. In the course of acute rheumatic fever, in a goodly number, the electrocardiographic changes

are reversible and may return to normal. When this sequence of events has occurred, the clinical interpretation is readily made that the pathologic process responsible for the particular change has resolved. Is there, then, any logical reason to assume that similar observations as to arrhythmias and T-wave changes, which occur in the course of other acute infectious disease in which non-specific myocarditis has been shown to occur, do not represent evidence of myocarditis? And when the electrocardiographic alterations in non-specific myocarditis return to normal, should it not likewise be interpreted that the inflammatory process responsible for the particular alterations has subsided? When the electrocardiographic change has become permanent, it is most likely that a permanent change has occurred in the myocardium.

As far as prognosis is concerned, most cases recover. Some die suddenly.[6, 17] Some show cardiac decompensation terminating in death.[4, 10] Saphir [17] recorded eight cases of bronchiectasis with myocarditis of which three died suddenly. In another paper he refers to Lisa, who reviewed the autopsies of 41 patients dying suddenly and found evidence of acute myocarditis in 36 cases.[1] From these observations one can conclude that when sudden death occurs in any disease associated with infection, the myocardium should be studied with great care to determine whether or not myocarditis is present.

The scheme which follows indicates the possible course of acute non-specific myocarditis of infectious origin. Acute non-specific myocarditis is always secondary to a primary disease of

I. Known etiology . . . . . (such as typhus fever, acute tonsillitis, etc., or of a recognizable entity such as infectious mononucleosis), with the result that the following takes place:
- (*a*) Recovery—Majority
- (*b*) Death —Minority
  1. Sudden
  2. With cardiac decompensation.

II. Unknown etiology . . . . . with the result that the following takes place:
- (*a*) Recovery—Majority—(as evidenced by electro-cardiographic alterations with no history of antecedent disease.)
- (*b*) Death —Minority—(Fiedler's myocarditis)
  1. Sudden
  2. With cardiac decompensation.

The treatment of myocarditis is symptomatic. Initially, bed rest is most important. The clinical signs, electrocardiographic changes, and the erythrocyte sedimentation rate should be used as criteria for the duration of the period of rest.

Discussion

The frequency of myocarditis has been stressed by a few clinicians and a few pathologists. Saphir, Wile and Reingold [23] found evidence of myocardial inflammation in 6.83 per cent of 1,420 autopsies on children. They encountered the same condition in 4.05 per cent of autopsies on 3,712 adults

during the same period. They state that the clinician diagnoses myocarditis rarely and the pathologist finds it more frequently. We agree that the clinician diagnoses it rarely, but if all the evidence in the literature on electrocardiographic changes in the course of acute or chronic infections be taken as evidence of an acute inflammatory process involving the myocardium (and we believe it is such evidence), the statement should be modified to say that the clinician finds it frequently, more frequently than the pathologist, but diagnoses it rarely. The reasons for the failure of clinicians to make such diagnoses have been mentioned above. We have apparently grown up in a period of medicine, in which the term myocarditis has fallen into profound disrepute.

It is probable that the incidence of myocarditis found at autopsy will be even greater when more care is taken by the pathologist in demonstrating the condition. Saphir has recommended taking many sections from the myocardium and examining them most carefully. Since acute myocarditis may involve the myocardium focally as well as diffusely, one or two sections cut by the microtome even from several blocks of tissue represent an infinitesimally small exploration of a relatively vast mass.

Aschoff nodules are found in only 80 per cent of cases in which acute myocarditis is demonstrated in hearts bearing the stigmata of rheumatic heart disease.[24, 25] In the 20 per cent in which no specific lesions are found, it appears necessary that the pathologic changes be more carefully evaluated. If there is no evidence of recent valvulitis, no evidence of proliferative changes in the endothelium of the smaller vessels, no evidence of Aschoff nodules elsewhere in the body, the diagnosis of rheumatic myocarditis should be made with caution. There is no reason to suppose that a rheumatic heart is immune to acute non-specific myocarditis. From a clinical standpoint, it is not rare following an acute upper respiratory tract infection to observe acute decompensation in a patient who previously had never decompensated or whose decompensation had been well controlled by therapy.

A correct appraisal of acute myocarditis is important. How frequently it occurs is not known. We are inclined to agree with Scherf and Boyd [11] who venture the assertion that with the frequency of infectious diseases and miscellaneous infections such as tonsillitis, etc., there are but few individuals who at some time or other do not have small inflammatory myocardial foci. If this is found to be so, myocarditis will have to be reëvaluated as one of the most common affections of the heart.

The frequency of the occurrence of acute myocarditis is not taken into consideration as much as it should be by investigators interested in establishing normal values for characteristics of the electrocardiogram. In a study of 100 cases of a prolonged P–R interval, Logue and Hanson [19] found 19 cases with no disease evident. They stated in summary that an occasional person may have a prolonged conduction time which is normal for that person. Graybiel et al.[26] found 16 instances among 1000 aviators of a P–R interval greater than 0.21 second. They stated that although P–R

intervals greater than 0.20 second should raise the question of past or present heart disease, they may indicate neither. Stewart and Manning [27] found 2.2 per cent of 500 healthy aviators with P–R intervals greater than 0.21 second in Lead II and 0.6 per cent greater than 0.24 second. They concluded that this number of normal males may be expected to have P–R intervals greater than 0.20 second. They also stated that this does not prove that they will not develop disease at a later time. At this point it must again be emphasized that prolongation of the P–R interval is a common abnormality seen in the course of many acute infectious diseases. This is commonly accepted as evidence of acute myocarditis when it is observed during acute rheumatic fever. It is likewise evidence of myocarditis in other infectious diseases. Prolongation of the P–R interval is reversible in many instances. In others it becomes a permanent characteristic. Where it is permanent, it is believed that some fibrosis has occurred along the conduction pathways. Since most of these instances of acute myocarditis are not recognized clinically, an observer taking routine electrocardiograms will collect a number of cases of prolonged P–R interval in apparently healthy individuals. The observers will naturally assume that these are normal variations. It is thus evident that a collection of cases studied statistically for P–R interval values may contain an internal bias. An alternate conclusion from the studies mentioned above might be that an abnormal atrioventricular conduction as evidenced by a prolonged P–R interval may be due to previous disease but is compatible with good cardiac function, as far as we know.

Weinstein [28] published 10 cases of *"Atypical" Coronary Disease in Young People* and emphasized the presence of antecedent acute infections. He invoked the possibility of a coronary arteritis as the underlying pathologic factor. In nine of the 10 cases the acute cardiac symptoms for which the patients were admitted followed from four days to several weeks after an acute infection. Five followed a "throat infection." Two followed "tonsillitis." One followed an "upper respiratory" infection. One followed a "pharyngitis." The precordial pain, electrocardiographic alterations and rapid erythrocyte sedimentation rate are phenomena also seen in acute myocarditis. The electrocardiographic patterns seen in anterior and posterior wall infarctions following coronary artery thrombosis are not pathognomonic of the underlying atherosclerotic process. Conclusions concerning the type of cardiac disease present cannot be drawn from the electrocardiogram alone.[29] It is thus possible that some of the cases reported as "atypical" coronary disease were in reality cases of acute myocarditis.

Scherf and Boyd [11] point out that occasionally in older patients it may be difficult to decide whether or not myocardial damage seen in the electrocardiogram is evidence of an old myocarditis, or secondary to coronary sclerosis. We have seen diagnoses made of acute rheumatic fever on patients without joint manifestations and without evidence of valvulitis, who had a continued fever and electrocardiographic findings of a prolonged P–R

interval. The electrocardiographic changes were interpreted as due to a myocarditis, which was reasonable. But the clinician failed to realize that a prolonged P–R interval due to myocarditis can exist outside of acute rheumatic fever.

Summary

Eleven cases of acute myocarditis, non-specific in nature, have been presented. The studies are entirely clinical. The reasons for the diagnoses are presented. Evidence is shown that myocarditis occurs more frequently than has been supposed. Some of the reasons for failure to recognize the condition are indicated. Acute myocarditis is discussed. The importance of a better understanding and a wider appreciation of acute non-specific myocarditis is stressed. It is pointed out that failure to appreciate the frequency of myocarditis may affect adversely some of the current research.

A case of acute myocarditis, following acute suppurative tonsillitis and eventuating in death, is described. As far as we know, this is the first case on record (proved by autopsy) of acute non-specific myocarditis following acute tonsillitis.

Conclusions

1. Acute non-specific myocarditis occurs more often than is generally appreciated.
2. The clinical diagnosis can be made more frequently than it is.
3. Acute non-specific myocarditis can follow acute suppurative tonsillitis.
4. Acute non-specific myocarditis was observed clinically in peritonsillar abscess, pneumonia, scarlet fever, gonococcal arthritis, urinary tract infection, infectious mononucleosis and typhus fever.

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MENINGOCOCCIC MENINGITIS TREATED WITH SULFADIAZINE AND SULFAMERAZINE: A THREE YEAR STUDY*

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MENINGOCOCCIC meningitis has been encountered with considerable frequency in the Gallinger Municipal Hospital as well as throughout the United States during the past few years. Previous reports from this clinic [1, 2] and from others [3, 4, 5, 6] have amply demonstrated the suitability of sulfadiazine and sulfamerazine for the treatment of this type of infection. The number of patients reported in each of these studies has been relatively small, however, or the period of time covered by them has been short. It still is pertinent to question the efficacy of these drugs when used in large numbers of patients treated over a longer period of time, and to study the factors which influence the prognosis in these patients.

In the present paper our purpose is to evaluate our results in the treatment of 207 patients with meningococcic meningitis who have been treated over a period of three years, between October 20, 1941, and October 31, 1944.

PROCEDURE

Routine procedures in the diagnosis and treatment of these patients have been carried out as follows: As soon as a patient believed to have meningitis was admitted to the ward, a lumbar puncture was performed. On the specimen of spinal fluid obtained several examinations were made immediately. A cell count and a Pandy test were done. Smears of the centrifuged sediment were made. They were stained with both methylene blue and Gram's stains. If organisms believed to be meningococci were seen, typing by means of the Neufeld technic was attempted. Cultures were planted in tryptose-phosphate or tryptose-phosphate-hemoglobin broth and on chocolate agar slants. A quantitative dextrose determination was made on the clear supernatant fluid by an application of Benedict's modification of the Folin-Wu method.[7] After this study had established a presumptive diagnosis of meningococcic meningitis and a blood culture had been obtained, treatment was begun. An initial oral dose of 6 grams of sulfadiazine or sulfamerazine was followed by 1 gram every four hours in adults. A proportionately smaller dose was given to children. For severely ill patients, especially those too stuporous to swallow, or for those who were vomiting excessively, the initial

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dose and a varying number of subsequent doses were given as a 0.5 to 1 per cent solution of the sodium salt of the drug intravenously or subcutaneously. The sulfonamide drug was continued until the patient was afebrile for approximately seven days unless some indication for stopping the drug developed sooner. Frequent hemograms, urinalyses and blood urea nitrogen and blood sulfonamide determinations were obtained during the period of drug administration. Follow-up lumbar punctures were done on the second hospital day and again when discharge was contemplated. If the cell count had not fallen to 30 cells per cubic millimeter the puncture was repeated at weekly intervals until the level was reached. At this time the patient was allowed out of bed and was subsequently discharged. Additional lumbar punctures were done only when the course of the disease was not progressing satisfactorily. Each spinal fluid specimen was examined in the same way as the one obtained by the initial lumbar puncture.

Patients who responded poorly to this régime in the first 24 to 48 hours were considered candidates for serum therapy, or, during 1944, for penicillin. After reëvaluation of the clinical status of the patient and the laboratory findings, serum was given intravenously if it was believed indicated. Penicillin was administered intrathecally in doses of 10,000 to 20,000 units. This was adjusted to a concentration of 1,000 units per cubic centimeter. The volume of diluted penicillin given always was 5 to 10 cubic centimeters less than the amount of cerebrospinal fluid withdrawn. The penicillin dose was repeated every 12 to 24 hours until satisfactory improvement was noted.

There was a total of 207 patients with meningococcic meningitis treated by this technic. The etiologic agent in every case was established by one or more of the following methods: (1) positive spinal fluid culture, (2) a positive blood culture in a patient with meningitis, or (3) a smear containing typical gram negative intracellular or extracellular diplococci. All cases of meningitis fulfilling these criteria were included in the present study and all others excluded. Patients with meningococcemia without meningitis were likewise omitted.

Meningococci were demonstrated in the stained sediment of the original specimen of cerebrospinal fluid from 188 (90.8 per cent) of our patients. They were present in sufficient numbers to make the diagnosis by means of the stained film alone quite certain in 134 patients, and to make it very probable in 54 patients. In many instances the diagnosis was confirmed immediately by direct Neufeld typing from the spinal fluid sediment. Whenever possible, the organisms were typed.* Among the 146 cases in which typing was successful, there were 136 patients with Group I, and 10 with Group IIa meningococcic infections.

Results

From table 1 it will be seen that 21 (10.1 per cent) of the 207 patients died. The case-fatality rate varied widely according to the age of the pa-

*We wish to thank Dr. Sara E. Branham of the National Institute of Health for typing many of these organisms.

TABLE I

Effect of the Age of the Patient and the Presence of Coma or Delirium Upon the Outcome in 207 Patients with Meningococcic Meningitis

Age	Total Patients Treated			Patients Admitted in Coma			
	Number Treated	Died		Number	Per Cent of Total Patients in the Age Group	Died	
		Number	Per Cent			Number	Per Cent
Total	207	21	10.1	94	45.4	20	21.3
0– 9	31	0	0	5	16.1	0	0
10–19	37	2	5.4	20	54.1	1	5.0
20–29	43	4	9.3	19	44.2	4	21.1
30–39	46	3	6.5	16	34.8	3	18.8
40–49	20	4	20.0	12	60.0	4	33.3
50–59	19	6	31.6	14	73.7	6	42.9
60–70	11	2	18.2	8	72.7	2	25.0

tient. In general it fell into one of three groups. Among patients nine years of age or less, there were no deaths. This is explained partly by our good fortune in not encountering any fulminating infections with the Waterhouse-Friderichsen syndrome in this age-group and secondly by the fact that there were only 10 children who were less than two years old. Our youngest patients were four, eight, eight and 10 months respectively. Six patients were in the second year of life. None of these very young patients was in coma at the time of entry.

The second group comprised patients in the second, third and fourth decades, in whom the case-fatality rate varied from 5.4 to 9.3 per cent. The third group included patients 40 years of age and over. The death rate for the whole group was 24 per cent and varied from 18 to 32 per cent. The relatively low percentage of deaths in the seventh decade can undoubtedly be explained on the basis of chance owing to the small size of the group.

In addition to age, the other important factor which greatly affected the outcome was the presence of coma or delirium. The death rate among the 94 patients with coma or delirium on admission was 21.3 per cent, whereas among the 113 patients who did not exhibit these manifestations only one patient (0.9 per cent) died. This patient was a girl of 15 years, suffering from a fulminating infection with the Waterhouse-Friderichsen syndrome, who died four hours after entry. Furthermore, among the 31 patients who had been in coma for 24 hours or longer before specific treatment was begun, 11 died, resulting in a still higher case-fatality rate (35.5 per cent).

In general, coma or delirium tended to be present more frequently among patients in the older age-groups, and the mortality rate in patients with coma or delirium rose progressively with age. Thus, the higher case-fatality rates in older patients might be explained partly by the higher incidence of coma or delirium, but they probably were also due in part to other and yet unknown factors that cause older patients to respond less well than do their younger co-sufferers.

Other findings of some prognostic significance were the presence, in the initial specimen of spinal fluid examined, (1) of dextrose in a concentration less than 10 milligrams per 100 cubic centimeters, or (2) of a large number of meningococci in the sediment after centrifugation. Among comatose or delirious patients with either or both of the above findings (table 2), the

TABLE II

The Effect of Delirium or Coma on Admission and of Many Cocci and/or Dextrose Levels below 10 Milligrams per 100 Cubic Centimeters in the Initial Specimen of Cerebrospinal Fluid on the Prognosis in 207 Patients with Meningococcic Meningitis

	Patients Treated	Patients Died	
		Number	Per Cent
Total Patients	207	21	10.1
Patients Rational on Admission	113	1	0.9
Total Patients with Coma or Delirium on Admission	94	20	21.3
Many Cocci,* Dextrose below 10	28	7	25.0
Many Cocci,* Dextrose 10 or above	15	4	26.7
Few Cocci or less,† Dextrose below 10	24	6	25.0
Few Cocci or less,† Dextrose 10 or above	27	3	11.1
Total Many Cocci *	43	11	25.6
Total Dextrose below 10	39	10	25.6

* Many cocci were recorded when at least one organism was seen in practically every field, and several organisms were seen in most fields.

† Few cocci were recorded when half of the fields contained no organisms, and relatively few organisms were present in any single field.

case-fatality rate was 25 per cent, whereas among 27 comatose or delirious patients in whose initial spinal fluids the dextrose level was above 10 milligrams per 100 cubic centimeters and organisms were few or absent, there were only three (11 per cent) who died.

The present series of cases confirms our previous observation that neither the presence nor absence of petechiae or of bacteremia, nor the height of the leukocyte count in the spinal fluid has any bearing upon prognosis in sulfonamide-treated patients.

COMPLICATIONS

Among the patients who recovered, the most frequent complications related to the infection were nerve palsies. These occurred in 35 patients. The majority of the palsies were present on admission or when they could be identified after a comatose patient regained consciousness. They involved both sensory and motor nerves. The most frequent sensory change noted was deafness which was present in some degree in 10 patients. In one of these, a child, deafness became apparent approximately one week after the patient had been discharged in what was thought to be good condition. In

one patient there was involvement of the fifth cranial (trigeminal) nerve with sensory changes in the face. Motor nerves were involved in 23 patients. These included the third (oculomotor), fourth (trochlear), sixth (abducens), seventh (facial), eleventh (spinal accessory) and twelfth (hypoglossal) cranial nerves. In one boy there was a temporary spinal nerve palsy resulting in a transitory foot drop. More nerves than one were frequently involved, the greatest number in any one patient being six. Although follow-up examinations of patients with nerve palsies have not been complete we have noted that little or no recovery occurred in a large majority of the patients who became deaf, whereas we have seen no patient with a motor nerve palsy that persisted for longer than six months after the onset of meningitis.

The other complications that we have encountered include 10 instances of arthritis or tenosynovitis and four of purulent conjunctivitis. All of these complications have been of short duration with no residual manifestations. In addition, one elderly patient developed extensive thrombophlebitis with secondary cerebral emboli and permanent mental deterioration.

Treatment

The basic treatment for all types of purulent meningitis is identical. This consists of (1) adequate sedation to keep the patient quiet and comfortable, (2) hydration, (3) sulfonamides and (4) nursing care. In our hands, morphine in full dosage has been the sedative of choice. It is the only sedative that will relieve the severe head pain suffered by these patients and thereby bring rest. Of equal importance is the adequate hydration of the patient. Practically all patients with meningitis are dehydrated from fever, vomiting, and failure to take fluids. It is of utmost importance to rehydrate the patients, that is to restore their fluid and electrolyte balance as rapidly as possible. It is important that the sulfonamide drugs be given well diluted so that the kidneys will be able to eliminate them without calculus formation. If the drugs are given parenterally, the initial dose should be in a concentration of 0.5 per cent or less.

The main specific therapeutic agent in all of our patients has been one of the sulfonamide compounds. Sulfadiazine was used for 112 patients of whom 13 (11.6 per cent) died. Sulfamerazine was used for 95 patients of whom eight (8.4 per cent) died. Two patients who were treated with sulfamerazine suffered clinical relapses while in the hospital. One patient, a female aged eight months, was treated again with a good response. The infant left the hospital in good condition. The other patient, a negro male aged 41 years, maintained a fever for 13 days after admission. No cause for the fever could be found and the spinal fluid showed only moderate abnormality. The sulfamerazine was discontinued and, since the patient became afebrile, it was thought that the episode had been drug fever. One week later, however, the temperature rose again and the patient showed a

pleocytosis of 4,000 cells in the spinal fluid. A test dose of sulfamerazine caused a sharp rise in temperature. The temperature remained elevated for 24 hours during which sulfadiazine was administered. Thereafter the patient was treated with sulfathiazole to which he made a slow but satisfactory response. A third patient, a white female aged 34, developed a toxic rash and fever after two days of sulfamerazine therapy. She then was given sulfadiazine to which she showed sensitivity reactions after four days. Her clinical condition was satisfactory and all specific medication was discontinued at that time.

Because some investigators have advocated that very high concentrations of sulfonamides be maintained in the blood, we have studied the relationship of the blood sulfonamide levels to recovery (table 3). Among 186 patients

TABLE III

Blood Concentration of Sulfadiazine or Sulfamerazine at Certain Times during the Course of Meningococcic Meningitis

Concentration of Sulfonamide in Blood, Mg. Per Cent	Number of Patients Showing the Indicated Blood Concentration			
	Concentration on the Day the Temperature Became Normal	Maximum Concentration Observed		
		Patients Lived	Patients Died	Total
0– 4.9	27	2	1	3
5.0– 9.9	64	43	2	45
10.0–14.9	48	61	3	64
15.0–19.9	15	43	4	47
20.0–24.9	6	18	1	19
25.0–29.9	3	11	2	13
30.0–34.9	0	4	0	4
35.0–39.9	0	1	0	1
No Record	23	3	8	11
Died	21	0	21	21
Total	207	186	21	207

who lived, there were 163 on whom sulfonamide levels were determined on the day the patient became afebrile. It is of great interest to note that 27 patients had levels of less than 5 milligrams per 100 cubic centimeters on that day. The lowest level so recorded was 1.6 milligrams per 100 cubic centimeters, and three patients had levels below 3.0 milligrams per 100 cubic centimeters. A total of 91 patients, almost 50 per cent of the patients who survived, had blood levels of less than 10 milligrams per 100 cubic centimeters, and only 24 had levels of 15.0 milligrams or above on the day their fever subsided.

The maximum blood levels obtained on each patient also have been tabulated. For two patients who lived and for one who died, the maximum level was below 5.0 milligrams per 100 cubic centimeters. Maximum levels below 10 milligrams per 100 cubic centimeters were found in 45 patients; maximum concentrations from 11 to 20 milligrams in 104 patients; and concentrations of above 20.0 milligrams in only 34 patients who recovered. The

relative frequency of the various maximum blood levels in patients who died was approximately the same as those obtained in patients who recovered.

This evidence confirms our point of view that it is not necessary to increase the dose of sulfonamides in order to obtain an arbitrary concentration in the blood as long as the patient's response is satisfactory. Furthermore, since toxic manifestations, especially renal calculi, are more frequently encountered when high concentrations of sulfonamides are present, it is not desirable to raise the dosage of these drugs unless it becomes necessary.

The toxic manifestations related to the administration of sulfonamide compounds have been comparable in every way to those reported elsewhere,[2, 8, 9] and need not be reviewed here.

Other specific therapy that has been used has been the administration of antimeningococcic serum or of penicillin. Serum was used occasionally in 1942 and 1943, being given to 11 patients. Two patients received serum, one intravenously and one intrathecally, in other hospitals before being transferred to Gallinger. The course of these two patients was in no way different from patients who received no serum. One patient who was admitted in diabetic acidosis was given serum as soon as the administration of the initial dose of sodium sulfadiazine was completed. The patient died within eight hours. Eight other patients received serum after having failed to respond to sulfonamide therapy in the first 24 to 48 hours. Four of these continued to fail and died. In two patients recovery definitely seemed to be related to the administration of serum, in that prompt improvement followed. In the other two patients who recovered, the actual value of the serum in influencing the outcome is questionable. Four of the six patients who survived after receiving serum developed mild serum sickness.

Since January, 1944, penicillin has been used in all patients who have failed to respond satisfactorily to sulfonamide therapy. Only two such patients have been encountered. Both were males, aged 47 and 41 respectively, who were in deep coma on admission. The initial cerebrospinal fluid showed many Group I meningococci in both. The dextrose level was less than 5 milligrams per 100 cubic centimeters in the first. It was not recorded in the second. Eighteen hours after admission the first patient had a temperature of 106° F. (rectal). He was markedly worse than on admission and was in peripheral vascular collapse. He received 25,000 units of penicillin intrathecally and after eight hours an additional 15,000 units. Thereafter he received 15,000 units intrathecally every 12 hours for a total of five doses. His response was dramatic. Within 24 hours his temperature fell permanently below 102° F., his respirations were regular and much less rapid, and he showed definite improvement. On the third day he began to respond rationally; on the fifth day he became afebrile. Thereafter his convalescence was uneventful.

The second patient also failed progressively but less dramatically. As a result his penicillin was started 34 hours after entry, and only 15,000 units

were given intrathecally. He continued to fail and died eight hours later. In this case the administration of penicillin may have been withheld too long.

Seasonal Incidence

Table 4 shows the effect of the time of onset of the disease as the epidemic progressed on the incidence, severity, and recovery. From January 1

Table IV

Comparison of the Seasonal Incidence of Meningitis with the Mortality Rate and the Duration of Illness

Season of Onset	Total Treated	Died		Average Duration of Fever * (Days)	Average Duration of Pleocytosis Spinalis † (Days)
		Number	Per Cent		
Jan.–June 1942	28	3	10.7	1.5	15.7
July–Dec. 1942	20	3	15.0	3.1	19.8
Total 1942	48	6	12.5	—	—
Jan.-June 1943	71	7	9.9	2.9	23.0
July–Dec. 1943	36	6	16.7	2.4	21.8
Total 1943	107	13	12.1	—	—
Jan.–June 1944	42	2	4.8	3.4	20.1
July–Oct. 1944	9	0	0.0	2.0	14.1
July–Dec. 1944	19	2	10.5	‡	‡
Total 1944	61	4	6.5	—	—

* From beginning of sulfonamide therapy until temperature permanently below 101° F. (rectal) in patients who recovered only.

† From beginning of sulfonamide therapy until the leukocytes were below 30 per cubic millimeter.

‡ Data not yet available.

to June 30, 1942, there were 28 patients. Fifteen of these were admitted in delirium or coma. There were three (10.7 per cent) deaths. From July 1 to December 31, 1942, there were 20 patients of whom 11 were admitted in delirium or coma. There were three (15 per cent) deaths. From January 1 to June 30, 1943, there were 71 patients of whom 33 were in delirium or coma. There were seven (9.9 per cent) deaths. From July 1 to December 31, 1943, there were 36 patients of whom 15 were in delirium or coma. There were six (16.7 per cent) deaths. From January 1 to June 30, 1944, there were 42 patients of whom 16 were in delirium or coma on admission. There were two (4.8 per cent) deaths. From July 1 to October 31, 1944, there were nine patients of whom three were comatose or delirious. There were no deaths.* Thus, there was no significant increase or decrease in mortality though there was a downward trend in 1944. It is interesting to note that in every year the mortality rate has been higher in the second half year than in the first half year, though in each instance the number of patients has been greater in the first half year. The rate of recovery as judged by the average duration of fever and of pleocytosis in the spinal fluid

* From July 1 to December 31, 1944, there were 19 patients with two (10.5 per cent) deaths.

showed a definite prolongation from January 1942 through June 1943, but following that there was a slight but definite decrease in the average length of illness.

Comment

In our previous report of 118 patients with meningococcic infections treated with sulfadiazine or sulfamerazine, we commented upon the low fatality rate observed, even though the group contained many patients in whom the prognosis might have been unfavorable. We have now enlarged our series to 207 consecutive patients with meningococcic meningitis treated by the same methods. The fatality rate for the entire group is 10.1 per cent, which is considerably lower than that observed in the presulfonamide days. Although the death rates reported from army and navy hospitals are lower than our figures, the difference is undoubtedly due to the fact that their patients are in a more favorable age-group and their treatment usually is instituted much earlier in the disease.

We have confirmed our earlier finding that the most important single factor in prognosis is the presence or absence of coma or delirium. Among the 113 patients who were rational on admission, only one died and she was suffering from the Waterhouse-Friderichsen syndrome. On the other hand, among 94 patients who were in coma or delirium on admission, 20 (21.3 per cent) died. Furthermore, among 31 patients who had been in coma or delirium for 24 hours or more before treatment was instituted, 11 (35.5 per cent) died. Thus, not only the presence but also the duration of coma is of great importance in determining prognosis in an individual case.

Another important factor in prognosis is the age of the patient. In general, the case fatality rate rose progressively as the age of the patients increased.

Of less significance in prognosis was the number of organisms and the reduction in dextrose in the initial specimen of spinal fluid. When either the number of organisms was high or the sugar was reduced below 10 milligrams per 100 cubic centimeters, the mortality rate in comatose patients was considerably increased. The presence or absence of bacteremia, of petechiae, or of a high leukocyte count in the spinal fluid had no bearing on the prognosis. Furthermore, there was no relationship between the concentration of sulfonamides in the blood and the outcome.

The epidemic of meningococcic meningitis which has been present in the District of Columbia as well as throughout the United States in the past three years has already shown evidences of being on the decline. We treated 61 patients in the year 1944 as compared with 107 in the previous year. For the years 1942 and 1943 the case-fatality rate in our series was slightly over 12 per cent, whereas in the year 1944 it decreased to 6.5 per cent. This is in accord with the generally accepted opinion that the severity of the disease diminishes toward the end of an epidemic. Although we found a slightly lower death rate when sulfamerazine was used than when sulfadiazine was

administered, this may have been due to the fact that sulfamerazine was used more extensively during the later stages of the epidemic. When a small group of patients was alternated between sulfadiazine and sulfamerazine, there was no appreciable difference in the results obtained.[2]

In a recent report [9] it is suggested that all patients with purulent meningitis be treated as one of the more serious varieties for the first 24 to 48 hours, pending a report from the bacteriologist giving the exact etiology. We feel that this practice is unnecessary and unwise. Among the 207 cases of meningococcic meningitis herein reported, a positive or presumptive diagnosis was made immediately from the direct examination of the spinal fluid in 188 (90.8 per cent) of the patients. Likewise, in a group of 56 patients with pneumococcic meningitis [10] we were able to obtain Neufeld typing directly from the spinal fluid in 42 (75 per cent). Furthermore, organisms resembling pneumococci, but in numbers insufficient for direct typing, were present even more frequently. Thus, if the centrifuged sediment of the spinal fluid is examined directly with Gram and methylene blue stains, a strongly presumptive diagnosis can be made in approximately 90 per cent of the patients with purulent meningitis.

Furthermore, an immediate examination of the spinal fluid is important because the severity of meningitis is directly proportional to the number of organisms seen in the original specimen of spinal fluid. This has been demonstrated for pneumococcic meningitis [10] as well as meningococcic meningitis, and in this clinic has been found to be equally true for all other purulent meningitides due to pyogenic microörganisms.

Summary and Conclusions

1. We have treated 207 patients with meningococcic meningitis during a three year period, using either sulfadiazine or sulfamerazine as the principal therapeutic agent. The gross mortality was 10.1 per cent. There was no significant difference in the case fatality rate in patients treated with the two drugs.

2. The number of patients treated, the case fatality rate, and the duration and severity of illness were less in 1944 than in 1943.

3. The etiologic diagnosis was established immediately from direct examination of the cerebrospinal fluid in 188 (90.8 per cent) of this group of 207 patients.

4. The factors of the greatest prognostic significance at the time of admission were the presence or absence of the coma-delirium state and the age of the patient. In patients who were delirious or in coma, the finding of numerous microörganisms in or the virtual absence of dextrose from the initial specimen of cerebrospinal fluid added to the gravity of the prognosis.

5. There was no relationship between the concentration of the sulfonamide in the blood and the outcome in meningitis. Massive doses of these drugs are not necessary for most patients with meningococcic meningitis.

Careful appraisal of patients and of the findings in the cerebrospinal fluid will indicate those patients who require more vigorous treatment.

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COCCIDIOIDOMYCOSIS IN SOUTHERN CALIFORNIA: REPORT OF A NEW ENDEMIC AREA WITH A REVIEW OF 100 CASES *

By Forrest M. Willett, Major, M.C., A.U.S., and Alvin Weiss, Captain, M.C., A.U.S.

War, and its attendant concentration of men in desert areas for training purposes, causes pulmonary coccidioidomycosis to assume increased importance. This influx of troops to sparsely settled regions carries with it an obligation for medical authorities to determine whether the infection is endemic in areas where military operations are in progress or contemplated. This seems obvious, in order that the disease may be readily recognized and proper treatment instituted from the onset, thus minimizing complications and loss of manpower.

Coccidioidomycosis may be briefly defined as an infection of the animal organism with the chlamydospores of the fungus *Coccidioides immitis*. By far the greater number of cases of the disease are of the pulmonary type, consequent to inhalation of the spores. Though infection through the skin has been adequately described, it is rare.[16, 27]

The disease in its progressive form was first described in the Argentine in 1892,[21, 31] and by Rixford in 1894 [22] on this continent in California. The life cycle of the parasite was first described by Ophuls and Moffitt in 1900.[19] The disease described by these early workers was termed coccidioidal granuloma and was known then, as now, for its somewhat macabre prognosis. In 1937, on the contrary, some 40 odd years after the original description, it was shown by Dickson and Gifford [6, 7, 12] that most cases of the disease are benign with a very good prognosis. The work of Dickson established beyond doubt the etiological relationship between *Coccidioides immitis* and "Valley Fever," and moreover, fulfilled the prediction made by K. F. Meyer [17] on purely theoretical grounds that a benign form of the disease should exist and would be found eventually. For further information concerning the development of this phase of the subject the reader is referred to those excellent articles of the original workers.[6, 7, 11, 12, 18, 19, 28]

The causative organism manifests two phases of reproduction. The so-called saprophytic phase, seen in cultures and presumably in nature, is considered to end in the production of spores called chlamydospores. Possibly these are formed under adverse conditions, as is the case of other spore formers. Certainly, large numbers of these chlamydospores appear in old cultures as the media dries out. Of its propagation in nature, very little is known. Soil cultures have been made successfully [5, 9, 30] but with some difficulty.[29] Smith and his co-workers [27] have examined the roots of vegetation

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from various soil levels in an attempt to obtain more evidence of the natural phases with no success. The soil of infected areas is almost always of an alkaline, calcareous type.

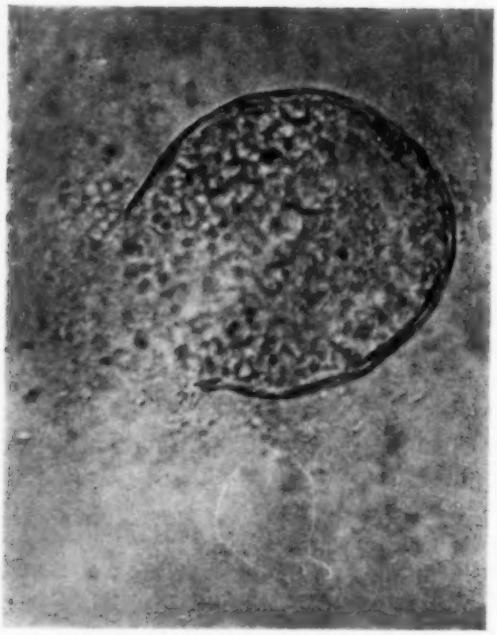

FIG. 1. (*Above*) Endospores rupturing from spherule.
FIG. 2. (*Below*) Dice-like chlamydospores.

The parasitic phase of the fungus is seen only in animal tissues and sputum or exudate,[27] and characteristically appears as a doubly refractile spherule containing endospores. Eventually these endospores burst from the parent spherule and in turn become spherules containing endospores.

The presence of these spherules in cultures of special strains of the organism has been reported by Baker and Mrak.[1]

Emmons [8, 9, 10] has demonstrated that a certain number of small rodents trapped in the Southwest were infected with *Coccidioides immitis* and also with *Haplosporangium parvum*.[10] Between these two fungi Emmons has shown some relationship, both by cross sensitivity to skin tests and the presence of microscopic lung lesions caused by *Haplosporangium parvum* in wild rodents and experimentally infected white mice. He feels that coccidioidomycosis is primarily a rodent disease transmitted to man only accidentally through the medium of dust contaminated with the spores by rodents. He also invokes the factors of host (perognathus, dipodomys) and climate to explain the lack of spread from the areas in which the disease is known to be present although these points are debatable. He suggests that in areas to be made the site of troop movements or other widespread activity, samples of the rodent population should first be examined for fungus infections.

Despite the fact that California has long been known to harbor the fungus in the San Joaquin Valley and other limited areas, it seems desirable to report a new and rather large endemic area as a guide to further studies in this region. Specifically, we should like to report that region, roughly triangular, bounded by Banning and Needles, California, and Yuma, Arizona, as a new endemic area for *Coccidioides immitis*. This desert region is spottily infected with the fungus of *Coccidioides immitis* and proof of this statement may be adduced from the following description of our studies in the area.

Epidemiology

From time to time, an occasional case of coccidioidomycosis had been seen on the Medical Wards of the March Field Station Hospital. Invariably these patients had acquired their infections in the San Joaquin Valley. Being suspicious of the desert and surrounding regions of the Southern California area,[16, 27] we began making routine skin tests using coccidioidin antigen on all patients with chest disease regardless of the suspected etiology. This applied particularly to the numerous cases of so-called primary atypical pneumonia being seen at that time. A careful travel history was taken on all positive reactors and special attention was paid to the itinerary and activities of the individual for the two months prior to hospital admission, with emphasis on assignment and activities in endemic or suspected areas. Obviously, a positive skin test in an individual who had always lived in a non-endemic area before coming to California was of greater significance than a positive reaction in a person from some known endemic region.

In April 1943, 12 colored soldiers were admitted to the hospital with acute pulmonary coccidioidomycosis. These soldiers were all from the same organization, engaged in a recently begun construction project near Banning, California.

Quite naturally, the possibility of proving a new endemic region suggested itself. The main effort consisted of repeated skin tests on 573 soldiers representing both colored and white troops, performing a dusty type of work at the edge of the desert. These intradermal skin tests were performed at periodic intervals between April 1, 1943, and July 26, 1943, using coccidioidin antigen in a dilution of 1:1,000. The antigen was furnished by Dr. C. E. Smith of Stanford University Medical School as part of the work of the Commission on Epidemiological Survey of the Board for the Investigation of Epidemic Diseases in the Army. One hundred and 35 "change overs" from negative to positive skin reactions were found, of which 83 were hospitalized with acute pulmonary coccidioidomycosis. The remaining 52 had insufficient findings to warrant hospitalization; however, these men were carefully followed and finally classified in the clinically inapparent group since no symptoms or objective findings ever appeared. The 135 cases which showed a change in the skin reaction from negative to positive (change overs) constitute the original epidemiological group by which the area of endemicity was established.

TABLE I

Troops in Survey Area

	Number	Percentage
White	214	37.3
Colored	359	62.7
Total	573	100.

TABLE II

Reactors in Original Epidemiological Group

	White		Colored		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Positive Skin Tests	47	22.	88	24.5	135	23.6
Hospitalized Cases (From Survey)	34	15.9	49	13.6	83	14.4

It is of interest to consider the incidence of infection in the two racial groups working in the desert under similar conditions. There were 214 white troops of whom 47, or 22 per cent, acquired positive skin tests in the area, of whom 34, or 15.9 per cent, were hospitalized. Of 359 colored troops 88, or 24.5 per cent, acquired positive skin tests, and 49, or 13.6 per cent, were hospitalized. In summary, 573 men were exposed, and 135, or 23.6 per cent, acquired positive skin tests, of whom 83, or 14.4 per cent, were hospitalized for acute pulmonary coccidioidomycosis.

Because of the above, the Surgeon General was notified on June 1, 1943, that according to the findings, a considerable part of the desert area was probably endemic for coccidioidomycosis.

In the eight months subsequent to the epidemiologic survey, 17 additional patients with acute pulmonary coccidioidomycosis have been hospitalized from the desert area, thus making a total of 100 hospitalized cases, almost equally divided between colored and white patients. In addition, during the year which has elapsed since the survey, one of us (FMW) has seen many patients with this disease in various hospitals throughout the desert and in those hospitals which serve as evacuation points for the desert. Moreover, civilian cases of coccidioidomycosis have been reported in this general area also with typical findings, including erythema nodosum and positive skin tests. Some of these civilian patients have been seen by us in consultation. These additional facts are offered as further proof to substantiate the epidemiological findings of the presence of the fungus.

Since all of the soldiers tested had been at March Field within three months prior to transfer to the desert, it was considered necessary to prove that the infection was not acquired at the Field. A control group was selected whose activities were confined to March Field or its immediate environs. Skin tests repeatedly performed on this group of 182 individuals over a six month period were consistently negative.

Diagnosis

The cases reported here presented no diagnostic problems. Eighty-three of them were hospitalized with a diagnosis as a result of the epidemiological survey, and 17 additional cases were hospitalized from the desert area. This is an unusual circumstance, quite different from the average situation confronting the Medical Officer in single cases. Of importance is a high degree of suspicion concerning this disease, if one is to make the diagnosis in individual cases.

The history is paramount, with reference to the residence, assignment, travel or recent activity in a known or possibly suspected area. The commonly accepted incubation time is from eight to 21 days, though the average is around two weeks.[5, 11, 23, 24, 25] Those accustomed to dealing with this disease are suspicious of its presence in any arid type of terrain, where long dry seasons and milder winters prevail. In general, the known endemic areas on this continent are portions of California, Arizona, New Mexico, Mexico and West Texas.[29] It is known to occur in Argentina and may well exist in other arid areas of the world. Rarely, cases of infection have resulted from merely passing through endemic regions by conventional transport.[23, 24] As might be expected, exposure and activity for somewhat longer periods of time usually result in a proportionately greater number of acute infections, especially in newcomers with occupations involving dust or work near the soil.[23] The occasional case occurring in individuals who have never been in an area even slightly infected is probably best explained by the accidental inclusion of a few chlamydospores along with some agricultural or other product derived from an endemic region.

Briefly, in any case with a pulmonary ailment and a history of recent travel in known or suspected areas, coccidioidomycosis should be considered in the differential diagnosis.

Symptomatology

Most authorities agree that by far the greater number of initial infections with coccidioidomycosis are of the inapparent or asymptomatic type. This is made evident by the intensive and illuminating work of Smith [23] in the San Joaquin Valley where large numbers of persons have positive skin tests and yet have never experienced an illness or symptoms which might be attributed to infection with *Coccidioides immitis*.

These cases reported here were also interesting in that many of the individuals comprising the series were hospitalized early, before the onset of symptoms of any magnitude. A few remained free of symptoms throughout the duration of the hospital stay, despite roentgenologic and serologic evidence of infection. However, symptoms elicited before and during hospitalization were essentially the same as those reported many times by others and were as follows:

Fever. Eighty cases, 80 per cent, had fever of some degree on admission, or after hospitalization, but the height and duration varied greatly. The temperature was usually remittent in character, and lasted in individual cases from one to 52 continuous days. The average duration of initial fever in white patients was four days, and in colored patients it was eight days. The absence of fever did not necessarily prove to be a good prognostic sign since many of the more severe cases remained afebrile throughout the greater part of their hospital stay, and occasionally, new evidence of activity would not be accompanied by a concomitant rise in temperature. As a concrete example of this, one patient developed the progressive form without any rise in temperature whatever.

Chest Pain. This symptom was present in 73 cases, 73 per cent of the series, and occurred in varying degree and location. Usually it was described as a feeling of tightness or constriction, more pronounced on the involved side, and aggravated by deep breathing or coughing. Ordinarily chest pain was not present after the acute stage; however, some few cases showed a persistence of the symptom, especially on exertion, for a period of months despite essentially negative physical, roentgenologic, and serologic examinations. Several cases showed definite localization of pain. One case in particular was suspected of having a fractured rib as a result of slight trauma to the chest a few hours prior to hospital entry. There was no fractured rib, but there was a pronounced pleural friction rub present.

Cough. This symptom was present in 64 cases, 64 per cent, and was, with rare exception, non-productive. In three cases, 3 per cent, the cough produced transitory blood-streaked sputum. The absence of sputum in most of the cases largely curtailed the use of sputum examinations as a means of diagnosis.

Joint Manifestations. Joint symptoms developed in eight cases, 8 per cent, at approximately four to 14 day intervals after hospital entry. Six cases, 6 per cent, were in conjunction with skin lesions and three of these cases had mild phlyctenular conjunctivitis.

The arthritis was characterized by moderate heat, very slight swelling, and much subjective complaint upon the smallest movements of the joint involved. Characteristically, several joints were involved, principally knees, ankles, and elbows, though no migration was observed. This symptom rarely persisted more than 10 to 12 days.

Cutaneous Manifestations. Erythema nodosum is one of the striking symptoms associated with infection by *Coccidioides immitis.* It has been used as a theoretical index by epidemiologists to compute the approximate number of cases occurring in a given region by using a percentage factor. Smith believes this cutaneous manifestation occurs in about 2 per cent to 5 per cent of infections.[5, 25, 29] In 135 infections of the original epidemiological group there were six cases or 4.4 per cent. All six cases had lesions over the tibial areas of both legs, characterized by reddish purple, tender, raised nodules in the skin, which recovered spontaneously leaving small areas of pigmentation for several weeks or months. All cases of erythema nodosum occurred in conjunction with joint symptoms. Two of the cases presenting joint symptoms and erythema nodosum were in colored patients. This was of sufficient rarity to demand further investigation, and upon questioning, it was found that both men had mixed ancestry.

Erythema multiforme was another cutaneous response seen in two cases, 2 per cent. This was confined to the face, neck, shoulders, arms, hands, and upper trunk, and occurred only in white patients. Neither case had any other skin lesion, nor did they have joint symptoms. The skin cleared in approximately seven to 10 days.

Urticaria was seen in two white cases, 2 per cent, and was of a generalized type, noteworthy because of severe pruritus, and our inability to allay the discomfort by whatever means attempted.

TABLE III

Incidence of Skin Manifestations

	Erythema nodosum		Erythema multiforme		E. nodosum and E. multiforme		Urticaria		Total Skin Manifestations	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
In the 135 cases composing the original epidemiological group.....	6	4.4	2	1.5	8	5.9	2	1.5	10	7.4
In the 152 cases composed of the original 135 plus the 17 additional cases hospitalized in the next 8 months.....	6	4.	2	1.3	8	5.3	2	1.3	10	6.6

Malaise. As a diagnostic feature too much emphasis should not be placed on this symptom. It was elicited in questioning, and in general covers the all embracing term often used by a colored soldier, "Ah jus' feels bad all over." Such a condition was present in 43 cases, 43 per cent. It was found in the early stages only, and did not persist longer than three or four days, though there were some exceptions to this general statement.

Anorexia. This was definite in 30 cases, 30 per cent, and persisted up to 10 days in a few patients, though as a rule appetite returned in full after four or five days. As a diagnostic symptom it was not helpful.

Headache. This symptom occurred in 27 cases, 27 per cent, and was definite. It was of a generalized nature in all cases. Several patients had headache of such severity that it was considered necessary to do spinal puncture, though no definite neurological symptoms were present. The spinal fluid was normal in all cases where puncture was done. The majority of cases with headache ceased to have this symptom after one week. There were, however, two cases in which the complaint persisted in severe degree for over a month, despite a complete neurological, otorhinolaryngological and roentgenographic study. The reason for this is not evident. Both cases were in colored soldiers.

Pharyngitis. This symptom was present in 20 cases, 20 per cent, with both the subjective complaints attendant thereto, and the objective findings of an injected moderately inflamed pharynx. This finding cleared rapidly in a few days after hospital entry, in no instance lasting longer than seven days. No exudate was described in any case. In 12 per cent barely palpable cervical glands were present. Smears and cultures of the throat were negative for significant organisms.

Chills. This symptom was present in 12 cases, 12 per cent, as a definite shaking chill. Not included were those whose description or findings were merely "chilly" sensations. Several patients with chills were actually observed on the wards and there can be no doubt about the quality of the chill. Numerous other patients related having "chilly" sensations.

Conjunctivitis was seen in only four cases, 4 per cent, and is only mentioned to complete the record. The cases so included were definite and occurred in connection with other manifestations described above.

Hemoptysis was seen in three cases, and was never more than mild blood streaking of the sputa. This symptom was only transient and was not particularly helpful diagnostically. It also is included for the record.

In conclusion, except for the persistence in a few cases of certain individual symptoms, as noted, the average case became asymptomatic, and usually experienced a rather pronounced feeling of well being in less than ten days.

Physical Examination

The physical examination in most instances is only moderately helpful as a definitive procedure. As may be judged, most of these patients are

obviously suffering from a respiratory infection and may have signs of fever, cough, and mild to moderate prostration at the onset. The pharynx may show a diffuse injection, but exudate was not seen in any of these cases. Examination of the chest may show signs of consolidation or fluid. Again, there may be a well localized pleural friction rub. Less than these easily identified physical signs, there may be a few râles, slight suppression of breath sounds or no perceptible variation from normal. Otherwise, unless there are skin or joint manifestations, the physical examination is usually not revealing. In the case of progressive or disseminated coccidioido-

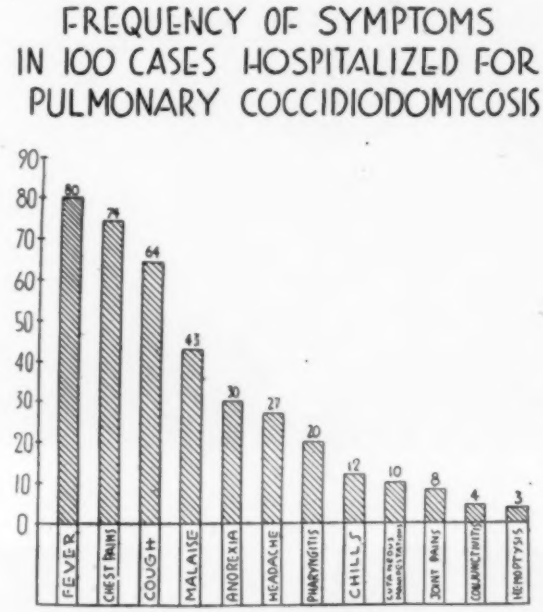

TABLE IV

mycosis, the skin or subcutaneous tissues may show nodules or small abscesses; again, there may be signs of meningitis, though we did not see this in any case.

ROENTGENOLOGICAL EXAMINATION

The roentgenogram was of great help both in diagnosis and in following the course of the disease. It is not the purpose of this paper to discuss the roentgenologic findings. For that the reader is referred to such excellent articles as those of Carter, Winn, and Colburn.[2, 3, 4, 32, 33] The roentgenologic findings for practical purposes may be roughly divided into the following categories:

1. Varying degrees of parenchymal infiltration, ranging from the most minimal lesion to that of consolidation.

2. Hilar adenopathy and thickening, not infrequently seen in connection with the parenchymal lesion.

3. Fluid, in varying amounts.

4. Nummular densities—single or multiple—usually in our experience indicative of old and focalized coccidioidomycosis.

5. Cavitation: This feature in all cases occurred as a late complication of the acute phase. The typically thin-walled cavity so often described was

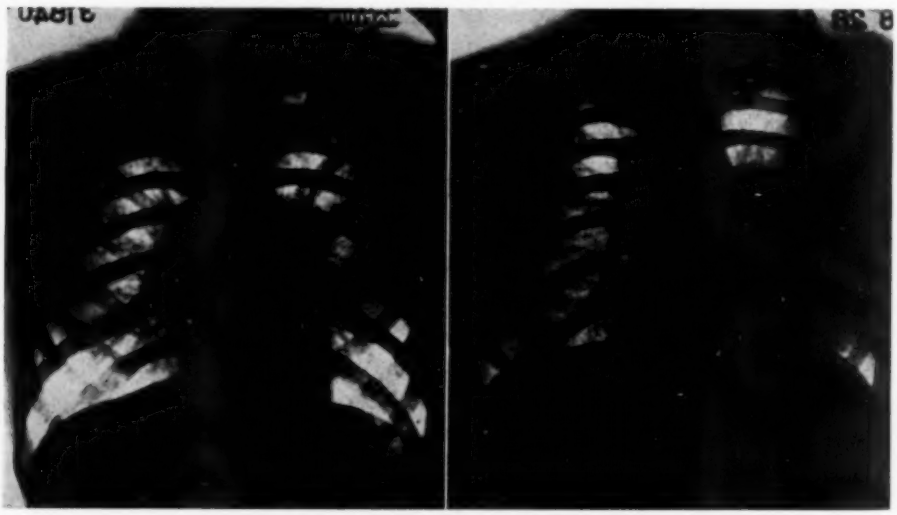

FIG. 3. (*Left*) Bilateral hilar adenopathy.
FIG. 4. (*Right*) Marked parenchymal infiltration in the left lung field.

FIG. 5. (*Left*) Left apical parenchymal infiltration similar to that seen in tuberculosis.
FIG. 6. (*Right*) Fluid filling the right pleural cavity.

FIG. 7. Cavity formation in fifth right interspace.

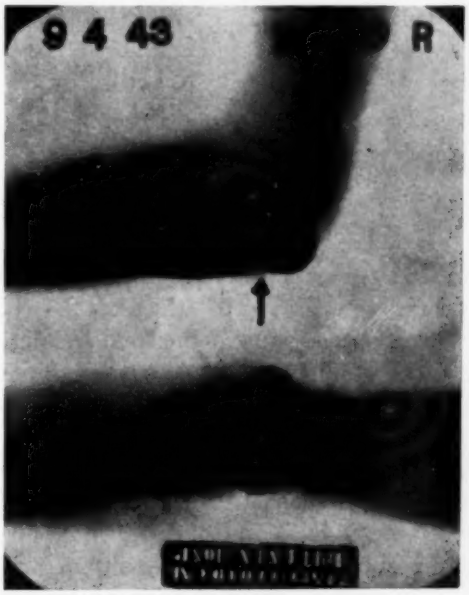

FIG. 8. Bone defect in ulna resulting from dissemination.

not seen as such at first. In serial films, cavitation occurred in a region which was the final area of consolidation, usually rather dense and well circumscribed. In the center of this area a rarefaction would appear, thus giving rise to a cavity surrounded by a relatively wide zone of residual reaction. Gradually, there was some narrowing of this peripheral zone so

that eventually a relatively thin-walled cavity remained. Usually these are found below the clavicle, and such was the case in all those cavities seen by us.

6. Bone lesions in roentgenograms showed well circumscribed areas of bone destruction, with some tendency to bone proliferation and elevation of periosteum. It so happened that the two bone lesions seen by us were in the proximity of joints at the end of long bones, though joint spaces were not invaded. It was impossible for us to follow the course of this type of lesion because these patients were transferred to Veterans Facility for long term care. However, with one exception, subsequent information received from the Facilities is of an optimistic tone.

Skin Test

This is probably the most helpful single test when used in conjunction with other aids, i.e., travel history, roentgenogram, sedimentation rate, differential blood count, and serological studies. The time required for the development of a positive skin test, according to most authorities, ranges from two days to four weeks. One case in this series required six weeks, which is unusual in the experience of most workers.[23, 25, 26] A recent previous negative skin test, followed in time by a positive one, is evidence of almost unquestionable validity in making the diagnosis. Kessel has shown that there is no cross sensitivity to tuberculin.[15] However, as mentioned previously, Emmons raises the doubt of cross sensitivity with *Haplosporangium parvum*.[10]

The generally advocated strength of antigen for routine testing is a dilution of 1 : 100.[25, 27] This is best if one has time only for one test and is willing to overlook the occasional large area of swelling and edema seen when using this strength. However, where coccidioidomycosis was suspected, and especially in hospitalized patients, we felt it was better to begin with a 1 : 1,000 dilution, and failing there, to use the 1 : 100. The optimal time for reading the skin test is 36 hours, but in the field, reading them at 48 hours was a more practical compromise. In the hospital skin tests are read at 24 and 48 hours, just as the intradermal tuberculin test. It is also very important to use new tuberculin syringes never before used for any other antigen in doing the skin test for *Coccidioides*. This avoids false positives by contamination with other antigens.[27]

A word of caution should be added concerning negative skin tests in persons with an illness showing features consistent with the diagnosis of coccidioidomycosis. Progressive or disseminated cases of the disease may have complete loss of sensitivity to coccidioidin antigen of any strength. It is here that sputum examinations, serological studies and biopsy are of value.

In summary then, failure to react to coccidioidin used as an intradermal skin test in a concentration of 1 : 100, rules out the possibility of coccidioidomycosis, except in those patients with disseminated infections, provided a sufficient time has elapsed to permit the individual to develop the sensitivity necessary to produce the reaction.

Blood and Serological Studies

These were represented by the differential total white blood cell count, erythrocyte sedimentation rate (Wintrobe), and serological studies with complement fixation and precipitin tests. The serological studies were done for us by the Commission on Epidemiological Survey in its study of coccidioidomycosis at the Stanford University School of Medicine.

The differential and total leukocyte count was of interest mainly because of the eosinophilia which appeared in these cases, and has been seen by others.[7, 27] On admission most patients showed some increase in eosinophiles, varying between 5 per cent and 18 per cent of the total leukocyte count. This ranged upward in subsequent counts during the second and third weeks of illness. In one patient, the eosinophile count rose to 30 per cent. There was a decline in the eosinophile count to normal levels in most cases after a maximum of four weeks, though in a few, moderate eosinophilia persisted up to six weeks. All cases of eosinophilia had at least one stool examination for parasites and ova, none being found. Briefly, polymorphonuclear increase of mild degree was seen in 35 cases, 35 per cent, ranging from 10,000 to 15,000. Sixty-four cases, 64 per cent, showed a white blood cell count under 10,000. One patient had a leukocytosis of over 20,000, and was at first considered to have lobar pneumonia because of the antecedent chills, fever, signs of consolidation confirmed by roentgenogram, and the white blood cell count. He was given sulfadiazine without effect, until the positive skin test became apparent in the ensuing 36 hour period.

The erythrocyte sedimentation rate was of considerable value. This was increased in all patients on admission and varied between 16 mm./hr. and 46 mm./hr. All expressions of this test reported here are corrected, using the Wintrobe method. The test was useful in both the diagnosis and the prognosis. Our practice was to have a normal sedimentation rate, along with other arbitrary standards, for at least 14 days before ambulatory privileges were given. Sedimentation rates were done at weekly intervals.

The serological studies were of inestimable value both in making a definite diagnosis and in following the course of the disease. There were a few cases which showed entirely negative precipitin and complement fixation tests, even though we had previously found a negative skin test, followed later by a positive one (change over), with roentgenologic signs of mild parenchymal infiltration, slight eosinophilia, and a sedimentation rate in the twenties. These were usually reported to us as having such a mild infection that it was insufficient to stimulate humoral antibodies. On the other hand, most of our cases showed definite serological reactions, with moderately high initial titer of precipitins, followed in turn by a variable though consequential titer by complement fixation.

It was of interest to us that Dr. Smith was able to predict in most instances, that certain patients were not doing well, or the converse, solely by serological tests. Dissemination was predicted before it occurred in every

case by the serological tests on the basis of high titers in complement fixation. This was regardless of the reaction to the skin test, which in one instance of dissemination, as previously mentioned, was completely negative. Needless to say, with such a record, we used the declining antibody titer as another index of safety in mobilization of the patient.

We have, in general, come to place a great deal of reliance in this relatively clear-cut test and only hope its early availability to all laboratories will bring it to the fore as a needed aid to diagnosis and prognosis for those treating this disease.

Sputum Examination

This examination consists of two phases.

1. Direct examination of a small amount of sputum mixed with 10 per cent sodium hydroxide on a slide with cover glass, after waiting a short time for clearing of the preparation. By this method, we were able to demonstrate a doubly contoured spherule containing endospores in 28 cases, 28 per cent. This examination requires experience and extreme care in interpretation.

2. Cultures of all sputa were made and were positive in 61 cases, 61 per cent. All cultures were not verified by animal inoculation, as a practical concession to our particular situation. Most cultures were kept until they were older and were then examined for chlamydospores, a particularly dangerous procedure and certainly not to be recommended. It is either a fortunate circumstance, or the result of unusual technic, that only one member of the laboratory staff became infected, developing a mildly positive skin test but no clinical signs of the disease. Such practice was discontinued instantly upon discovery.

All sputa were examined a minimum of six times by both direct and culture methods for tubercle bacilli and none was found in the entire series by either method.

In general, our impression of the sputum examination in the diagnosis of coccidioidomycosis is that it is not an entirely satisfactory method. Certainly it is helpful, but the failure to find or cultivate the organism does not exclude the diagnosis, and the culture method is slow, dangerous, and to be absolutely certain, requires animal inoculation as a final measure. Our best results with sputum examinations were obtained by using sputum coughed up in the early morning, after the patient had rinsed the oral cavity with 50 per cent alcohol solution.

In summary, the following factors are important in the diagnosis:

1. History of recent exposure to dust in a known or suspected endemic area.
2. Symptoms and physical findings as outlined above.
3. Positive skin test.
4. Elevated sedimentation rate.

5. Roentgenologic findings in the chest.
6. Serological findings.
7. Eosinophilia (need not be present).
8. Sputum examination, direct and culture.

In the final analysis, a presumptive diagnosis could be made in those patients who came from a known or suspected endemic area with signs of a respiratory infection and a positive skin test. If in addition, there was roentgenologic evidence of lung or hilar involvement, the diagnosis was probable. Definite diagnosis could be made in cases showing the above with positive serological studies, biopsy or animal inoculation with recovery of the organism. A recent change-over in the skin test from negative to positive would fall in the last category.

Complications

Cavitation and dissemination are the two main complications in our experience. The latter is of far greater importance than the former although probably less frequent.

Cavitation. Cavitation of the lung occurred in six cases, 6 per cent, four of which were in colored, and two in white soldiers. Smith [25, 26, 27] considers cavitation no menace to the patient, either present, or future, the lesion being a "focalization" of the disease which excavates more or less mechanically. Such patients are generally considered resistant not only to exogenous, but to endogenous infection as well. The cavity, if old, is usually a thin-walled anatomical defect in the lung parenchyma, or if recent may be surrounded by a zone of increased density, presumably representing residual reaction in the area from which it formed. Such a cavity, the result of coccidioidal infection, is almost always a "silent" one. Rarely hemoptysis is seen, or if complicated by secondary infection or tension effects, symptoms may arise. Conservative treatment such as absolute bed rest, sandbagging the affected side of the chest, or tight strapping, will in a goodly percentage of cases be rewarded by closure.[27] Pneumothorax is successful in a certain number.[27] Surgical measures such as lobectomy, seem inadvisable in most instances, though there may be exceptional circumstances where such could be applied with benefit.[20, 27] It seems wiser, however, to exhaust less radical measures before operation is attempted, especially when dealing with so-called "silent" cavities. Also of some importance, and in contradistinction to cavities of tuberculous origin, those patients with coccidioidomycosis cavities are not a menace, either to themselves or their associates in that they are non-infectious.[20] Spontaneous closure may be seen. A brief discussion of end results so far as observed in our cases seems worthwhile.

Two cases of cavitation in white soldiers showed favorable end results. One case (number 1) in which the original cavity measured 1.75 centimeters in diameter, cleared entirely leaving a small residual fibrosis in the lung parenchyma. This case required 144 days, 102 of which were hospital days,

and 42 of which were on out-patient status, before closure of the cavity was effected. After the acute phase of the disease, he was free of symptoms for the entire time. Subsequent observations for three months showed him to be well and in good health, with the chest roentgenogram reported essentially negative. The second patient, whose outlook is equally optimistic, had a one centimeter cavity in the right lower lung parenchyma, which was presently closing, but had not completely done so after 61 days of hospitalization. He was asymptomatic and was on a bed rest regimen, aided by strapping and sand bags to the right lower chest, for whatever benefit may accrue from this measure.

Four cases of cavitation occurred in colored soldiers. In general, the results achieved by hospitalization were less favorable than with the white group, although identical hospitalization and attention were given to both. The following are colored cases.

Three cases of cavitation were transferred to Veterans' Facility for further hospitalization. This was considered necessary because of lack of satisfactory general progress as evidenced by fever at intervals, fast sedimentation rates, and serological titers of a high dilution, as well as the persistence of cavity by chest roentgenograms, with no tendency to close. One of these cases disseminated to bone, which was added reason for the transfer. These three cases had four months of military hospitalization under optimal conditions.

The fourth case was of considerable interest. This colored male after hospitalization for acute pulmonary coccidioidomycosis, ran the usual course, with findings clinically and roentgenologically of a severe case. Serological studies showed confirmatory high titers. Sedimentation rates were elevated, and sputa were positive for *Coccidioides immitis,* and negative for *Mycobacterium tuberculosis* on several direct examinations.

After 30 days of hospitalization a cavity, one centimeter in diameter, developed in the right second interspace anteriorly on chest roentgenograms. He was returned to light duty after 90 days of hospitalization, inasmuch as his condition fulfilled the standards that had been set for return to duty, namely, clinical well being, normal sedimentation rate, static or declining serologic reactions, and a roentgenogram which showed a static lesion, in this instance the small cavity. All studies for tuberculosis were negative, including gastric lavage with guinea pig inoculation.

Ten weeks later, after being observed at intervals in the out-patient department, he was readmitted to the hospital because of fluid in the right pleural cavity. Physical examination was essentially negative save for signs of fluid in the right chest. Chest roentgenogram confirmed this, and the persistence of the cavity in the right upper lobe. The sedimentation rate was 24 mm./hr. (Wintrobe corrected). During the early part of this hospitalization there was an occasional rise of temperature to 99° F., but this was normal otherwise.

Thoracentesis was performed, with aspiration of 650 c.c. of straw-colored fluid, containing 100 per cent lymphocytes. The specific gravity was 1.020. Direct examination of the fluid was negative for bacteria or fungi. A guinea pig inoculated with the fluid showed no evidence of tuberculosis or coccidioidomycosis. Serological study showed a slight decline in titer from the previous hospital entry, indicating that the infection was being well handled. A tuberculin skin test (purified protein de-

rivative) first strength was negative, but the second strength showed a two plus positive. No sputum was produced at any time, though gastric lavage samples again inoculated into a second guinea pig were reported negative for both tuberculosis and coccidioidomycosis.

The further course of this case was uneventful, being characterized by absorption of the pleural fluid and closing of the cavity. The chest roentgenogram reported only a moderate blunting of the right costophrenic angle, with slight residual fibrosis in the area of the cavity. The sedimentation rate was normal (8 mm.) after the first month of bed rest. He was returned to duty after 60 hospital days, free of symptoms and apparently well. Subsequent observation for three months found this patient well and in good health with no essential abnormalities in the chest roentgenograms, or other laboratory data, except for the persistence of a moderately high serological titer, and even this was on the wane.

It can rightly be argued that the pleural effusion was possibly, or even probably, on a tuberculous basis and not coccidioidomycosis at all. It is our feeling, however, that the fluid was on the basis of coccidioidomycosis. He is being observed at monthly intervals for any change of status.

In summary then, two cases of cavities in white soldiers either closed or showed strong tendency to close at the last examination. Of four cases of cavitation in negroes, only one closed and that after a rather unusual course involving pleural effusion. The three remaining cases of cavitation in colored men have been transferred to Veterans' Facility for long term treatment, one case being of a disseminated type. Three of the six cases of cavitation, regardless of racial incidence, will undoubtedly be on full military duty in a short time, whereas the three remaining cases were lost to the military service. The question might be raised as to why we did not use pneumothorax. This is a form of long term therapy which was considered inadvisable in a station hospital. It is the opinion of this staff that the end results would not have been markedly different in the event this procedure had been instituted. That, however, is debatable.

Disseminated or Progressive Coccidioidomycosis

The disseminated form is by far the most serious type of infection by *Coccidioides immitis*. In this form, the prognosis is considered poor, with usually less than an even chance of recovery. The chances of dissemination, statistically,[25] seem rather small, since large surveys made by Smith [11, 28] show a rate of dissemination of about one in 500 cases. Small as this figure might seem, it none the less urges caution and conservatism in the treatment of uncomplicated cases of acute pulmonary coccidioidomycosis. Any attitude less than this may well reduce the favorable prognosis associated with the uncomplicated form.

Despite the conservative treatment accorded the patients in this series, the disseminated form occurred in four cases, 4 per cent, all of which were in colored soldiers at complete bed rest. Of the 49 colored patients represented in this series, this represented a 12 per cent rate of dissemination, a figure almost unbelievably high. Moreover, it confirms strongly what has long been known, namely, that the dark skinned races handle this disease poorly.[27]

It would seem worthwhile in the light of this to consider carefully the areas into which colored troops are being sent, particularly if the area is known or suspected as an endemic one for this fungus. A brief discussion of the four disseminated cases follows, though no extensive data are presented.

Of the four cases, one ended fatally (see below), with a generalized miliary dissemination, involving virtually every organ and system of the body except the gastrointestinal tract and central nervous system. Of the other three, two cases had dissemination to bone, and the last disseminated to muscle. The latter case was proved by biopsy of the muscle tissues, revealing typical spherules of *Coccidioides immitis*. In those patients showing bone involvement no attempt was made to biopsy the bone lesions, for in the presence of clinical, serological, and roentgenologic findings there seemed no doubt of the validity of the diagnosis.*

Treatment and Criteria for Return to Duty

Treatment. The average case of acute pulmonary coccidioidomycosis has an extremely good prognosis for complete recovery. Barring dissemination or complicating cavitation, the average case is almost in the class of a self-limited disease, given proper treatment. There is no "specific" for the disease.[27] Simple measures such as aspirin, codeine in small doses, or other mild analgetics are usually quite sufficient to handle the acute symptoms of the disease. Vaccines have been used with questionable results. Roentgen-ray has been suggested, though no large series has been reported using this agent. Immunotransfusions from patients with high titers of antibody have been used by us and others,[14] with no convincing results. Surgical excision has been used on local abscesses caused by the fungus, and reported favorably,[14] though further exploration of this measure is in order.

The main essential of treatment is adequate bed rest, and until the patient is markedly improved this should be absolute bed rest.[27] Once the patient has been mobilized, his eventual disposition is a problem facing all medical officers attending such cases. The following standards for return to duty were established and used at this hospital on all cases reported here.

Criteria for Return to Duty. (1) The patient must be clinically well, with freedom from symptoms and fever for at least three weeks, and preferably one month.

(2) The chest roentgenogram should show a relatively clear picture, or at least minimal findings with no evidence of activity for one month. The term activity is used to denote either improvement or extension of the chest lesion. Practically, one could not hope to keep some of these cases until the chest was reported clear, for many carry residual nummular densities or slight fibrotic reactions for months or even years. If the chest roentgenogram showed the lesion to be static and minimal, and the patient had reached

* Since this has been written, correspondence with the Veterans' Administration reveals that one of the cases of bone dissemination has disseminated to other bony structures, so that he now has three distinct areas involved.

what seem like maximal benefit from hospitalization, the other laboratory factors noted below being in keeping, we felt safe in returning that man to light duty for periodic observation at monthly intervals. In no instance did this produce any seriously adverse results.

(3) The sedimentation rate should be within normal limits on at least two weekly intervals and preferably for three weeks or one month.

(4) There should be no evidence of increased activity as shown by serological studies. Although it was desirable to see a decline in the serological reaction, practically it was necessary to be content in some cases with a static or slightly declining titer.

(5) There should be no evidence of dissemination.

Despite these precautions, one colored patient developed evidence of a disseminated lesion to bone one week before he was scheduled to return to duty. He was retained in the hospital and transferred to Veterans' Facility for further care. No dissemination occurred in any patient who was returned to full duty, and it is our impression that rigid adherence to the criteria as outlined most certainly helped in avoiding dissemination.

Presentation of Illustrative Cases

The following cases have been chosen because they illustrate different aspects of pulmonary coccidioidomycosis. The first is that of an average case with complete recovery, the second is one in which pleural effusion occurred, and the third is a case of dissemination to muscle. The last patient illustrates a case of progressive coccidioidomycosis which ended fatally.

The following is an illustrative average case.

The patient was a well developed, well nourished, 36 year old white male, who entered the hospital on May 16, 1943 because of hoarseness, chest pain, and nonproductive cough of two weeks' duration. He had been in the desert area for about one week before the onset of these symptoms. His temperature on admission was normal but physical examination revealed an urticarial rash over the legs and thighs. The pharynx was mildly injected and breath sounds were increased at the left base. His white blood cell count on admission was 11,400 with 72 per cent polymorphonuclears and 5 per cent eosinophiles. Roentgenogram of the chest revealed parenchymal infiltration extending from the left fourth rib anteriorly to the diaphragm and from the heart border to the chest wall.

The day following admission into the hospital the patient began to have fever which continued for the next 13 days. A coccidioidin skin test 1:1,000 dilution was positive and blood was sent to Stanford University for serological investigation. Eight days after his entrance into the hospital the urticarial rash extended over the chest and abdomen and persisted for four more days. The sedimentation rate was 18 mm. on admission, went as high as 28 mm. during the first month of illness and gradually receded to 13 mm. two weeks before discharge.

Serial roentgenograms of the chest revealed a gradual resolution of the original parenchymal infiltration until June 7, approximately three weeks after admission, when evidence of bilateral infiltration was noted. This too showed gradual clearing until June 23 when a new area of infiltration was seen in the second right interspace. At about this time the white blood cells rose to 14,100 with 31 per cent

eosinophiles. Following this there was a gradual clearing of the involved areas and on discharge the roentgenogram was considered essentially negative. Sputum examinations revealed no coccidioidal spherules on wet slide preparation, but culture on Sabouraud's media gave a growth suggestive of *Coccidioides immitis*, which was subsequently proved by animal inoculation. Repeated examinations of 12 specimens of sputum failed to reveal any tubercle bacilli on either smear or culture. Stools were negative on repeated occasions.

Serological tests performed June 26, 1943, were as follows:

Complement Fixation: Negative in all dilutions.

Precipitin Tests: Serial Dilutions of Antigen

Undiluted	1:10	1:40
++++	++++	++

These results were interpreted as characteristic of a primary coccidioidal infection as yet well focalized.

Approximately two months after admission the patient was given modified ambulatory privileges. He continued to remain afebrile and asymptomatic and was gradually allowed to extend his activities in the Army Air Forces Rehabilitation Program. He was subsequently sent to duty on August 3, 1943, after approximately 80 days of hospitalization and after fulfilling all the criteria for return to duty.

This patient was observed for approximately three months after his return to duty from the hospital, and during this time repeated physical examinations and chest films were essentially negative. Sedimentation rates and leukocyte counts were within normal limits. He had no complaints and is now doing full duty.

Pleurisy with Effusion

Pleurisy with effusion occurred in five, 5 per cent, of the cases. This complication was seen in three white patients and two colored patients, or in 6 per cent of the white group and 4 per cent of the colored group. The effusion, with one exception, occurred early in the course of the acute phase of the disease. Three of the effusions were present on admission, one occurred 15 days after hospitalization, and the fifth came on approximately five months after cavity formation. Although four of the five cases had massive effusions, there was no evidence of respiratory embarrassment. Thoracentesis was done on these four cases of effusion, and what fluid was not withdrawn was rapidly absorbed.

Examination of the fluid removed from the chest revealed a specific gravity in keeping with an exudate (1.022), and a marked preponderance of lymphocytes. Smear and culture with guinea pig inoculation was done routinely, and the fungus was recovered in one patient.

The following is a case of pleurisy with effusion:

This patient was admitted to the hospital on June 22, 1943. Skin test for coccidioidomycosis on June 12 was negative but was two plus on June 19, 1943. During the course of the epidemiological studies he was discovered to have a white blood cell count of 18,400 with 5 per cent eosinophiles. His sedimentation rate was 16 mm. and chest roentgenogram was reported as showing an increased prominence and fuzzy density about the right hilum with generalized increase in the markings, more pronounced in the right lower lung field. There was also hazy density with irregular and poorly defined borders in the right costophrenic angle.

Because of the above findings, the patient was admitted to the hospital for treatment. On entrance the patient stated he had experienced some mild right-sided chest pain for the past two weeks and night sweats and fever for the past week. Physical examination revealed a well developed, well nourished, white male of 21 who was not acutely ill. His temperature on admission was 99.2° F., and examination of his chest revealed no abnormal findings except for slight suppression of breath sounds at the right base.

The patient was put on symptomatic therapy including bed rest, and except for a slight amount of fever, got along fairly well until July 7, his fifteenth day of hospitalization, at which time physical examination revealed evidence of a right-sided pleural effusion. This was confirmed by roentgenogram. At this time the white blood cell count was 12,000 with 9 per cent eosinophiles and the sedimentation rate rose to 30 mm. On July 22, about two weeks after the effusion was first noted, thoracentesis was done, with the removal of 600 c.c. of a straw-colored fluid. Smear of this fluid revealed spherical bodies with endospores typical of *Coccidioides immitis*. This was subsequently confirmed by culture and animal inoculation.

Repeated sputum examinations for *Coccidioides immitis* and tubercle bacilli were negative. Serological tests for *Coccidioides* gave the following results on June 25, 1943:

Complement Fixation:	1:2	1:4
	++	+
Precipitin Tests:	Undiluted	1:10
	++++	+

Interpretation: Findings characteristic of primary coccidioidal infection as yet well focalized.

Following thoracentesis the patient made a gradual and uneventful recovery. Roentgenograms of the chest showed a gradual clearing of the parenchymal lesion and absorption of the remaining fluid. Sedimentation rate returned to normal on August 9, and eosinophilia went down to 2 per cent before return to duty.

On August 17, serologic tests were repeated with the following results:

Complement Fixation:	1:2	1:4
	+++	+

Precipitin Tests: Negative in all dilutions.

Interpretation: This indicates a definite trend toward complete recovery.

The patient was returned to duty on September 15, 1943, with chest films reported as negative and all criteria for discharge fulfilled. Patient was observed in our Chest Clinic for three months after return to duty, and during this time he had no complaints. The sedimentation rate remained normal, and serial films of the chest were negative.

Dissemination

As was previously mentioned, dissemination occurred in four of the colored patients, and did not occur in any of the white soldiers. Of the four cases, one terminated in death, one disseminated to muscle, one to bone, and one to both muscle and bone.

The muscle lesions occurred as small, firm, relatively painless intramuscular nodules about one to two months after the onset of symptoms. Bone lesions, on the other hand, were introduced by the sudden onset of pain and tenderness over the involved area. These occurred approximately three to four months after hospitalization.

The following is a case of dissemination to muscle.

A well developed, well nourished, colored male of 28, entered the hospital on May 21, 1943 complaining of headache, cough, chills, and fever of four days' duration. Patient was a laborer with a unit that had worked on construction in the desert area from April 24 to May 14. On admission his temperature was 102.8° F., with respiration rate of 22 and pulse of 96. Physical examination revealed occasional moist râles and increased breath sounds at right base. Roentgenograms of the chest revealed infiltration of moderate density over the lower half of the right lung field. The white blood cell count was 16,100 with 74 per cent polymorphonuclears, 21 per cent lymphocytes, and 5 per cent eosinophiles.

Because of the sudden onset with headache, cough, chills, and fever, accompanied by a high white blood cell count and roentgen-ray findings of infiltration, the patient was put on sulfadiazine therapy. This was discontinued in 48 hours when he showed no response to clinically effective blood levels, and because skin test for coccidioidomycosis was positive (two plus) in 1:100 dilution. At no time did he appear toxic in spite of a swinging type of temperature curve suggestive of a bacterial infection.

On June 7, 1943, he was given a 250 c.c. blood transfusion from a convalescent case of coccidioidomycosis with moderately high titer in serological studies. On the following day a transfusion was given from another convalescent patient also with moderately high titer. No particular or specific benefit accrued as a result of these transfusions insofar as we were able to determine. He continued to run a swinging febrile course for 41 consecutive days, following which he remained essentially afebrile except for an occasional rise to 100° F.

On June 28, 1943, the patient developed a small pea-sized subcutaneous nodule on the lateral aspect of the left lower leg. Biopsy revealed evidence of an acute inflammatory reaction of undetermined etiology. On July 14, a one-half centimeter, firm, non-tender nodule developed in the left deltoid muscle. Biopsy of this nodule revealed typical spherules containing endospores.

Serial roentgenograms of the chest revealed an extension of the original inflammatory process in the right middle and lower lobes during the first 10 days of hospitalization, and then a gradual clearing of the process. Sputum examination revealed typical coccidioidal bodies on June 10, some 21 days after entrance into the hospital. In the early stages of the disease the white cell count reached a height of 19,000, and after a short period of fluctuation it came down to 9,500 with 3 per cent eosinophiles. His sedimentation rate remained about 38 mm. throughout most of his hospital stay.

Serological examinations were made at frequent intervals and showed the following:

On June 7, 1943:

Complement Fixation:	1:2
	+++
Precipitin Tests:	Undiluted
	++++

Interpretation: Findings indicate a primary coccidioidal infection as yet well focalized.

On June 14, 1943:

Complement Fixation:	1:2	1:4	1:8
	++++	++	+
Precipitin Tests:	Undiluted	1:10	1:40
	++++	++++	+

Interpretation: Findings characteristic of primary coccidioidal infection as yet well focalized. (Titer slightly higher than previous specimen, but not alarmingly so.)

On July 27, 1943:

Complement Fixation:

1:2	1:4	1:8	1:16	1:32	1:64	1:128
++++	++++	++++	++++	++++	+++	+

Precipitin Tests:

Undiluted	1:10	1:40
++++	++++	+

Interpretation: The titer of complement fixation is now in the range of disseminated infections.

A titrated skin test at this time showed the following:

	24 hrs. Positive	48 hrs. Positive
Dilution 1:1,000	¾" diam.	1" diam.
1:100	¾ × 1" diam.	1½" diam.
1:10	1½ × 2½" diam.	2½ × 3" diam.

On Aug. 13, 1943:

Complement Fixation:

1:2	1:4	1:8	1:16	1:32	1:64
++++	++++	+++	++++	++++	+++

Precipitin Tests:

Undiluted	1:10
++	++++

Interpretation: The titer of complement fixation continues to rise, indicating that dissemination is also continuing.

This patient remained in the hospital until September 9, 1943, representing 111 hospital days, during which time he developed another subcutaneous nodule in the right epitrochlear region. He was transferred to a Veterans Facility for further care. A letter from this Facility stated that the patient was discharged on October 13 after an uneventful and asymptomatic hospital course. A roentgenogram of the chest taken during his hospitalization at the Veterans Facility showed further resolution of the inflammatory process in the right lower lobe. His sedimentation rate was reported as 9 mm. The eventual outcome of this patient will be of interest.

The following is a fatal case of disseminated or progressive coccidioidomycosis with autopsy.

A well developed, well nourished, colored male of 21 years, entered the hospital on March 25, 1943, because of precordial pain and palpitation of two weeks' duration, and chills, fever, and cough of two days' duration. Examination revealed a temperature of 101.4° F. (orally), pulse 22, respirations 22. The pharynx was moderately injected and the breath sounds were roughened over the right base where an occasional transient râle could be heard. There were no other abnormal physical findings.

His white blood cell count on admission was 8,900 with 66 per cent polymorphonuclears, 30 per cent lymphocytes, 4 per cent eosinophiles, and 1 per cent monocytes. Chest film revealed an increase in density along the right upper mediastinum in the first and second interspaces suggesting a possible primary atypical pneumonia. An electrocardiogram was normal except for an inverted T-wave in Lead IV. A tentative and questionable diagnosis of primary atypical pneumonia was made although tuberculosis, fungus infection, and early Hodgkin's disease were considered and had to be ruled out. Several sputum examinations for significant organisms were entirely negative.

The patient was put on symptomatic therapy and continued to show a septic temperature ranging from 99° to 103° F. daily. Coccidioidin skin tests were negative in 1:1,000 and 1:100 dilutions on repeated occasions. Tuberculin skin tests using O.T. tuberculin in a strength of 1:10,000, 1:1,000, and 1:100 were also negative.

During his illness the patient was given a course of sulfadiazine and sulfathiazole therapy with no response. He also received three blood transfusions from patients convalescing from primary atypical pneumonia, but none of them had any effect on his clinical course. During all this time the patient clinically did not appear to be as sick as his temperature curve indicated.

Meanwhile, his white blood cell count rose from 8,900 with 3 per cent eosinophiles on entrance, to 16,300 and 26 per cent eosinophiles. Serial chest films showed an infiltration extending into the third right interspace anteriorly with marked increase in prominence and density about the right hilum and gradual infiltration into the right apex.

On April 10, 1943, numerous small discrete subcutaneous nodules developed over the trunk. Similar nodules of a larger size developed on the medial surface of the left lower extremity. None of these was painful; all were firm and seemed to be attached to or a part of the underlying tissue. There also appeared some small pustular lesions on the face.

By this time the patient was beginning to bring up a moderate amount of sputum, and examination of this sputum revealed the spherules of *Coccidioides immitis*. At this time also a skin nodule was biopsied and revealed the presence of *Coccidioides* as proved by culture and guinea pig inoculation, as well as by pathological section of the material removed.

The patient became progressively worse, his temperature ranged from 104° to 105° F. daily, and the respiratory rate rose to 50 per minute. On April 22, 1943, a portable roentgenogram of the chest revealed a marked extension of the pneumonic process involving almost all of both lung fields. The nodular type of increased density in the right upper and middle lobe showed a tendency to become confluent so that complete consolidation was present. Consolidation was also present in the left lung from the apex to the fourth interspace. Despite active supportive therapy the patient became moribund and died on the twenty-ninth day of hospitalization.

Autopsy. General: The body showed good muscular development and nutrition. Scattered throughout the subcutaneous tissues of the face, scalp, and extremities were firm and at times fluctuant nodules measuring three to five millimeters in diameter. These were most numerous on the face and scalp where some of them had broken down and discharged their contents. Similar nodular masses were palpated in the muscles. The lymph nodes of the axillae and groin were enlarged and firm. There was a fluctuant mass in the region of Virchow's node which measured 1.2 cm. in diameter.

Respiratory System: In each pleural cavity there were 500 c.c. of straw-colored fluid. The pleura was glistening throughout. Both lungs were dark purple in color with many yellowish, firm, slightly round nodules scattered over the surface. The lungs cut with ease. The cut surface showed patchy areas of consolidation. The surrounding parenchyma was congested and frothy blood-tinged edema fluid could be expressed from the surface. Anteriorly both lungs were crepitant to palpation. The bronchi contained frothy edema fluid. The tracheobronchial lymph nodes were markedly enlarged, the largest measuring 2 by 3 by 5 cm. On section they were composed of necrotic grummous material.

Cardiovascular System: The pericardial sac contained 200 c.c. of straw-colored fluid. There was a 1 by 2.5 cm. area of subpericardial hemorrhage over the apical portion of the left ventricle. There were a few scattered yellow miliary nodules on the visceral pericardium. The remainder of the heart was negative.

Aorta and Great Vessels: Essentially normal.

Spleen: The spleen was markedly enlarged, weighed 700 grams, and measured 11 by 15 by 6 cm. It was quite soft on palpation and pulp oozed from the cut surface. Scattered over the capsular and cut surface were the same small yellowish necrotic nodules. The trabecular structure and malpighian bodies were indistinguishable.

Liver: The liver weighed 2,470 grams. The surface was completely covered with nodular areas similar to those seen in other organs. On section they were found scattered throughout the parenchyma which was congested.

The gall-bladder, biliary duct system, pancreas, and adrenals were grossly normal.

Genitourinary Tract: The right kidney weighed 285 grams and the left 240 grams. Their capsules stripped with ease, revealing the same scattered miliary abscesses. On section the cortical and pyramidal markings were distinct except where obliterated by the small abscesses.

The pelvis, ureters, bladder and testicles were grossly normal.

Skull and Central Nervous System: On removing the scalp the above mentioned abscesses were found to lie in the subcutaneous tissues and did not involve bone. The dura mater, dural sinuses, and arachnoid membrane were normal. There was congestion of the cerebral vessels. The convolutions of the brain were flattened and the sulci obliterated. No other pathological change was found in the brain.

Muscles: Many of the above mentioned subcutaneous abscesses extended down to involve the fascia and the underlying muscle.

Microscopic Examination. Lungs: All sections of the lung showed scattered areas of fairly dense fibrous tissue which were irregular in size and shape. Some of these resembled tubercles in their structure, having a central area of epithelioid cells surrounded by a wide zone heavily infiltrated with round cells, macrophages, and at times polymorphonuclear cells. In many of these areas, there were seen large spherical bodies, having a diameter of 10 to 18 micra, a thick hyaline capsule, and a large central zone filled with small endospores. These bodies were typical of *Coccidioides immitis*. The surrounding parenchyma showed thickening of the alveolar septa due to infiltration of round cells and macrophages and some increase in fibrous tissue. Many of the alveoli contained large numbers of macrophages and a few were filled with purulent exudate. A number of the alveoli showed partly hyalinized plugs in the process of organization. Similarly many of the small bronchioles were filled with plugs of well organized fibrous tissue which was infiltrated with round cells and macrophages and occasionally the specific organism.

Microscopic sections through the heart, spleen, liver, adrenals, kidneys, and lymph nodes showed similar scattered areas which were pathologically similar and varied only in size and numbers. This consisted of a central area of necrosis, surrounded by an inflammatory zone infiltrated with round cells and macrophages and accompanied by a minimal fibrotic reaction. The organism of *Coccidioides immitis* could be demonstrated in many of these granulomatous nodules.

Pathological Diagnosis. 1. Coccidioidomycosis, disseminated, with abscesses of the lungs, spleen, liver, kidney, adrenals, lymph nodes, subcutaneous tissue and muscle. 2. Pneumonitis, diffuse, organizing. 3. Congestion, passive, generalized.

Summary

Reference to the tabulation of end results shows the disease to be preponderantly more severe in colored persons. The hospital days were high, a finding in keeping with most others reporting on the subject. The number of hospital days in colored soldiers was almost twice that of white soldiers.

We should be remiss if we failed to mention the Convalescent and Rehabilitation Program of the Army Air Force Hospitals. This was of dis-

TABLE V

Summary of Complications and End Results in 100 Cases Hospitalized for Pulmonary Coccidioidomycosis

	White	Colored	Total
Total Cases	51	49	100
Cavitation	2	4	6
Effusion	3	2	5
Dissemination	0	4	4
Death	0	1	1
Separated from Service	2	4	6
Hospital Days (Case Average)	55.7	99	
Hospital Days	2832	4846	7678

tinct benefit to both patients and doctors in such a long term hospitalization program.

1. A new endemic area in Southern California has been reported for *Coccidioides immitis.*

2. A series of 100 cases of acute pulmonary coccidioidomycosis has been reported with end results as far as observed over one year.

3. Complications and illustrative cases have been presented.

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THE PATHOLOGY OF SICKLE CELL DISEASE*

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The incidence of the sickle cell trait among North American Negroes has been estimated from various surveys to be 7 per cent,[23] 7.2 per cent,[10] 9.1 per cent [6a] and even as high as 13 per cent [1a] of the Negro population. Clinical sickle cell disease appears in an undetermined fraction of cases in which the trait is present, estimates of this ratio varying from 1 : 7 to 1 : 40.[23] As far as can be determined the trait is transmitted as a true Mendelian dominant,[12, 15, 23, 33] independent of the inheritance of blood type.[23] This apparent fact has been used as an argument that the trait is limited exclusively to Negroes, and that sicklemia in white persons [21, 23] is pathognomonic of Negro ancestry.[23] There is some evidence, however, that this disease may have existed in Mayan Indians,[20] which suggests the possibility that the mutation responsible for the abnormality may be capable of repetition independently in another race. In any case the estimated 135,000 sufferers from the disease in the United States are almost entirely Negroes.[23]

The disease exhibits a chronic hemolytic anemia which is usually manifested by acute exacerbations superimposed upon relatively quiescent periods.[1, 5, 18] These episodes are characterized by severe joint, muscle and abdominal pains, fever and other constitutional symptoms, and massive hemolysis with jaundice.[5] The mechanism of these hemolytic crises has not been determined. A search of the literature has disclosed no reported case in which the crises were studied over a period of time adequate to establish their characteristics and periodicity.

The purpose of the present paper is to describe the pathology of sickle cell disease and to outline a concept of the mechanism underlying the development of the hemolytic crises.

We studied a patient with sickle cell disease for 12 months, 30 weeks at St. Luke's Hospital and the remainder of the time at Goldwater Memorial Hospital. This case presented in all respects the characteristics typical of sickle cell disease as described in the literature. Investigations of the behavior of the erythrocytes have been reported in a previous communication.[22]

Case Report

A 21 year old, male, unmarried Negro was admitted to St. Luke's Hospital on November 29, 1942, complaining of generalized muscle and joint pains, especially in the large joints but also in the ribs and along the spine. The diagnosis on admission was acute rheumatic fever and rheumatic heart disease. The patient had had frequent and severe attacks of what were believed to have been episodes of acute

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rheumatic fever since the age of three years, and he had been in bed for seven weeks previous to admission because of the symptoms which eventually brought him to the hospital.

He was rather slight, but otherwise not remarkable in general appearance. The mucous membranes, palms, and soles were pale. Increased pulsations were evident in many of the peripheral arteries, especially about the rami of the jaw. The patient appeared in moderate discomfort, with pains in both ankles, the calves, right shoulder, anterior chest, and back. The temperature was normal, but the pulse rate was 120. The heart appeared slightly enlarged to the left, with a somewhat forceful apical impulse 11 cm. from the mid-line in the fifth left interspace. There was a blowing systolic apical murmur and a suggestion of a presystolic murmur, neither of which was well transmitted away from the apex. The rhythm was regular and the other sounds were of good quality. The lungs were clear. The spleen could not be felt but the liver was enlarged 2 to 3 cm. below the costal margin. Some tenderness was found about the affected joints, and in the calves and muscles of the thighs and shoulders. There were several small dark scars on the shins, presumably remnants of old healed ulcers. There were no gross bony deformities except for the fifth fingers of both hands, which were shortened, owing to dwarfed metacarpals. The sclerae and the contour of the retinal vessels showed none of the abnormalities previously described in sickle cell disease.[14, 16]

The first blood count after admission established the diagnosis of sickle cell disease. During the first 10 days the clinical picture continued unchanged, with a low grade fever and migratory pains. Thereafter the patient's course was characterized by the so-called "active" and "latent" [35] phases alternately of sickle cell disease. Altogether there were seven "active" periods. Five of these were very similar in type, and occurred in the form of dramatic crises. The remaining two assumed a less striking pattern, resembling more the picture of activity presented during the first 10 hospital days. Of the total number of 214 days spent at St. Luke's Hospital, 79 were manifested by obvious activity of the disease, and 135 days were apparently "quiescent." The illness was thus actively manifested 36.9 per cent of the time. During the quiescent periods the patient was clinically quite unremarkable. He appeared simply as a frail young man with the physical signs delineated above, who was moderately active and who carried trays and did useful chores about the ward.

The typical crisis (of which there were five) would start suddenly, so that within the space of about two hours, the patient would be transformed from a cheerful and active young man into a victim of very severe and widely disseminated joint and muscle pains. As these pains commenced the patient would lie on his bed with his extremities in semiflexion, and protest against all attempts to move him. The pain was so severe that morphine in ¼ grain (.015 gm.) doses repeated every three or four hours usually afforded only slight relief during the first two or three days. There was marked tenderness in the various painful regions, most frequently in the anterior thigh muscles, knee joints, shoulders, and right hip, but occasionally also about the thorax. Although abdominal pain sometimes occurred, there was never acute abdominal tenderness and spasm, or nausea, vomiting, and diarrhea, to suggest the well known "abdominal crises" [36] of this disease.

Pain was in every case the first symptom of a crisis. It was invariably followed by a rise in temperature commencing 4 to 24 hours later, the average duration of this febrile interval being 16½ hours. The peak of the fever would usually be reached within 24 hours of its onset. Despite its frequently rapid rise, it was never associated with a chill. By the third to the fifth day the pain and temperature would begin to subside together. The first sign of remission was usually the observation that morphine succeeded in relieving the pain. At about the same time the temperature would start to recede, and the patient would steadily improve thereafter. By about the

eighth day the crisis was over, and by the tenth to eleventh day the patient would usually be up helping about the ward again.

The above described pattern represents the clinical behavior of five crises which were so strictly similar that they may be taken to represent the "typical" crisis. There were two other crises of less sharply defined pattern in which the only constant clinical feature was the precedence of fever by pain. Also there were occasional periods of ill defined activity, such as the first 10 hospital days, and three other attacks of pain with or without slight fever, lasting from a few hours to one day.

The asymptomatic periods between the crises lasted from 10 to 27 days, the average intercritical period being 16.7 afebrile days. On the average a crisis would start every 26⅔ days, the extreme intervals between their onset being 20 to 36 days. The crises lasted for from 7 to 10 days, the average duration of the seven reported crises being 8.4 days. Two crises merged into moderately extensive though relatively symptomless episodes of pulmonary consolidation which we believe to have been caused by infarcts. These were accompanied by fever and slight cough, but otherwise did not bother the patient. The last, and severest crisis, was complicated also by congestive heart failure and gross pulmonary edema, so that for two days it appeared that the patient would not survive.

A typical crisis began on February 3, 1943. The associated laboratory findings are illustrative of all the crises studied, both typical and atypical. The clinical course lasted eight days and was as described above. Throughout almost daily determinations the hemoglobin and red blood cell levels were seen to fall gradually throughout the crises from 10.6 gm. per 100 c.c. and 3.0 million red blood cells to 7.7 gm. and 2.4 million red blood cells respectively. One week later these levels had recovered to 9.5 gm. and 2.9 million respectively, and by the end of the third week (near the beginning of the next crisis) the values were fully restored, being 10.8 gm. and 3.5 million respectively. These last figures represent the "peak" values for this patient, as his erythrocytes never rose any higher. The serum icterus index became elevated during the crisis. On the first day of the crisis its value was 8. On the third and eighth days it was 20. Two days after the end of the crisis it had returned to a reading of 10. Although the icterus index often ranged between 18 and 20 even during the quiescent periods, it regularly rose higher during the crises. During two severe crises the patient was grossly jaundiced.

Hemolysis during the last crisis observed by us was so rapid and severe that in the space of six days the hemoglobin dropped from 10.3 gm. per 100 c.c. of blood to 6.6 gm., and the red blood count from 3.4 to 2.1 million per cu. mm. This is a destruction of 36 per cent (from the fall in hemoglobin) or 38 per cent (from the fall in red blood cells) of the total erythrocyte elements of the body in six days, an average of 6 per cent of the body's red cells being destroyed per day.

The erythrocyte sedimentation rate showed no significant variation from normal during the crises, except for two high values of 76 and 110 respectively in the first two weeks, the maximum normal being 20 mm. per hour.

The leukocyte count increased from 8,850 per cu. mm. with a differential count of 41 per cent polymorphonuclear leukocytes and 54 per cent lymphocytes during an inactive phase, to 19,000 with 80 per cent neutrophiles during one crisis, and 34,000 with 89 per cent neutrophiles during another.

Each crisis presented striking laboratory evidence of bone marrow stimulation. Thus the reticulocyte count, which at no time ever dropped below 5 per cent, rose during the crises to as high as 31 per cent. *It was noted on smears that the reticulocytes never appeared in sickled form.* Large numbers of normoblasts always appeared, amounting to as much as 40 per cent of a nucleated cell count of 22,000. The normoblasts rapidly disappeared from the circulation following each crisis, and would be absent or rare by the third symptom-free day. It was noted that normoblasts also

did not sickle. Blood smears showed other manifestations of immaturity, such as diffuse and stippled polychromatophiles and Howell-Jolly bodies. The leukocytes, in addition to becoming elevated with each crisis, reflected bone marrow stimulation in a very marked regenerative shift to the left. On several occasions myelocytes appeared. During the last recorded crisis true myeloblasts were found in large numbers on three successive blood smears. These reached a concentration of 7 per cent of a white count of 22,000.

An apparent increase in the number of sickle cells was observed in chamber counts near the beginning of each crisis. Direct smears made of both arterial and venous bloods during a quiescent phase showed that 5.4 per cent of the red cells were sickled, and, on the first day of a crisis that 10 per cent were sickled, the venous blood showing slightly more deformed cells by this method than the arterial. Although this method is crude, it appears to yield useful results in that the arterial and venous smears were within fairly close limits on each determination. Thus for the first count the arterial blood showed 48 abnormal forms in 1000 cells and the venous 56. In the second the figures were: arterial 91 sickled cells, venous 116.

The hematocrit value, which was 30.5 per cent of packed red blood cells during the quiescent phase, had dropped to 26 per cent just after a crisis. There was a slight increase in the red cell volume index (1.07–1.1) and decrease of the hemoglobin saturation index (0.98–0.95) at the end of a crisis. These variations may be within the limit of laboratory error, but they are in any case characteristic. The color index remained constant (1.04) throughout three determinations.

The fragility of the red blood cells to hypotonic saline was reduced during both active and quiescent phases, hemolysis being very imperfect at a concentration which completely hemolyzed the control cells.

The test for urobilin which was constantly present in the urine, was qualitatively increased during the crises. (Quantitative measurements were not undertaken.) Bilirubin was never found in the urine.

A skin and muscle biopsy taken from a tender area in the left anterior thigh on the first day of a crisis, and fixed in formalin, showed capillaries, venules, and arterioles in the muscle to be crowded with, and slightly distended by sickled erythrocytes and a delicate fibrin meshwork.

Other laboratory data are of interest though not related specifically to the crises. Roentgenograms of the skull afforded extraordinary evidence of a chronic hemolytic anemia, in the demonstration of marked thickening of the tables over the vertex and a ray-like "hair on-end" arrangement of the trabeculae. Spotty decalcification of the long bones was also seen. Roentgenograms of the right hip demonstrated irregularity of the femoral head with flattening and eburnation suggesting aseptic necrosis due to impairment of the blood supply to the region, presumably as a result of thrombosis. The chest film showed moderate enlargement of the heart especially in the region of the left ventricle.

The urine consistently showed a few casts and traces of albumin. Signs of kidney insufficiency were revealed in a fairly fixed specific gravity and an inability to concentrate to a higher specific gravity than 1.010. There was also hematuria on at least one occasion.

The blood platelets varied by direct counts between 200,000 and 400,000. The total protein content of the blood was consistently normal. An electrophoretic analysis of the plasma will be discussed later in this paper. The Mazzini blood serological test was negative. The blood levels for urea nitrogen, non-protein nitrogen, and uric acid were not remarkable, being 10.0, 20.0, and 4.5 mg. per 100 c.c. of serum respectively. The vitamin C level of 0.83 mg. per 100 c.c. rose to 1.5 mg. following administration of ascorbic acid. The serum alkaline phosphatase was normal, being 3.4 and 4.4 Bodansky units on two determinations. The blood cholesterol was 222

mg. per 100 c.c. The van den Bergh reaction was direct, positive, delayed. A gastric analysis yielded normal free HCl. The serum calcium was 11.4 mg. per 100 c.c. The CO_2 content of the venous blood was 49 volumes per cent.

Electrocardiograms showed progressive T-wave changes throughout the period of hospitalization. The first tracing showed no abnormalities other than sinus tachycardia. There was a gradually increasing left axis deviation throughout the patient's course, and progressive inversion of the T-waves until they were finally abnormal in four leads. There were no significant changes in the P–R interval. The changing electrocardiogram reflected progressive cardiac damage which culminated clinically in congestive heart failure and pulmonary edema near the end of the patient's hospital course.

Epistaxis was noted on four occasions during the period of observation.

Among the therapeutic agents employed, iron and blood transfusions were directed against the anemia, but wholly without success. Ferrous sulphate was given in dosages amounting to 1 gram daily for an uninterrupted period of three months, with no demonstrable effect on the red blood elements. Two transfusions, each of 500 c.c. of whole blood, were followed by no change, or a very transient rise, in the hemoglobin and red blood cell count. The first of these transfusions was followed by an abrupt temperature rise to 104° F., with a gradual fall to normal over a 48 hr. period. The second transfusion was given at the height of a crisis, so it is impossible to tell whether or not it caused a similar reaction.

In summary, the picture is one of chronic hemolytic anemia of a severe degree, manifesting itself by "active" and "latent" phases. Abnormal blood destruction is evident at all times, including the "quiescent" phase, as reflected by the persistent hyperbilirubinemia. During one hemolytic crisis 37 per cent of the red blood elements were destroyed in six days. Compensatory bone marrow hyperplasia is so far advanced that it accounts for striking roentgenographic findings. The chronically elevated reticulocyte count rises further during crises, and large numbers of nucleated erythrocytes are released into the blood stream. The crises are also characterized by dramatic onset and course of 8 to 10 days, and by a severe constitutional reaction. They are associated not only with blood destruction and regeneration, but also with a high leukocytosis. Although the red blood picture as a whole is one of marked poikilocytosis and anisocytosis, the anemia remains strictly normocytic and normochromic. Iron would therefore not have a rational basis as therapy. There were also noted progressive myocardial damage and renal involvement throughout the patient's course.

Electrophoresis Study

An electrophoretic analysis of the patient's plasma during a quiescent period demonstrated an A/G ratio of 1.12, excluding fibrinogen. The pattern showed that 47.4 per cent of the total protein was albumin, 7.9 per cent alpha, 11.0 per cent beta, and 23.4 per cent gamma globulin, and 10.3 per cent fibrinogen. A chemical analysis showed the total protein of the plasma to be 8.8 per cent. The low A/G ratio is not uncommon in disease states. Longsworth, Shedlovsky, and MacInnes [42] have reported low values in a variety of diseases, such as aplastic anemia, rheumatic fever, pneumonia, peritonitis, peritonsillar abscess, acute lymphatic leukemia, lymphogranuloma, obstructive jaundice, lipoid nephrosis, and myeloma. It would be interesting to learn whether it is consistently found in sickle cell disease. The content of gamma globulin is definitely high, being approximately 50 per cent of

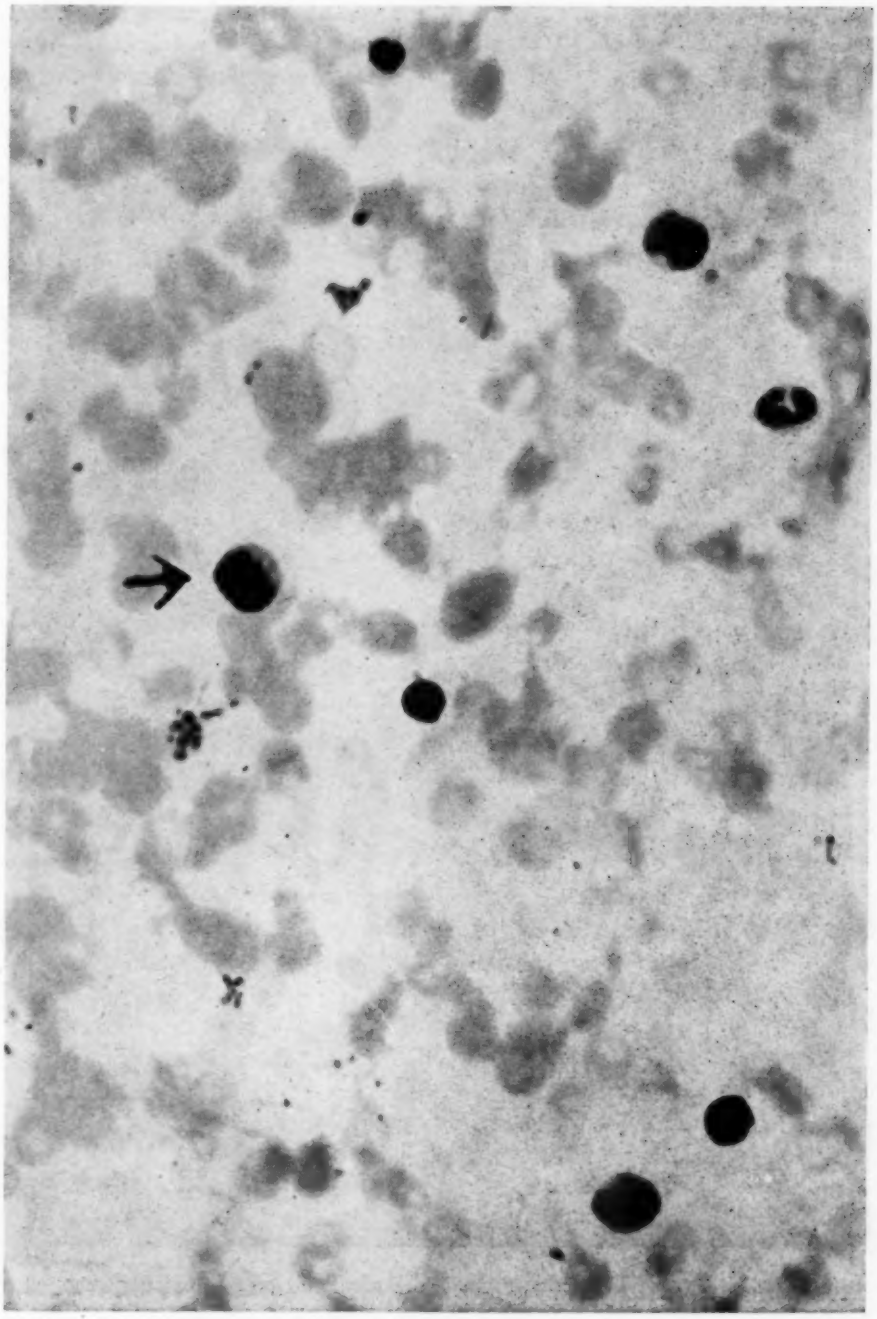

FIG. 1. Blood smear obtained during crisis showing myeloblasts. Arrow indicates typical myeloblast. Magnified 1,000 ×.

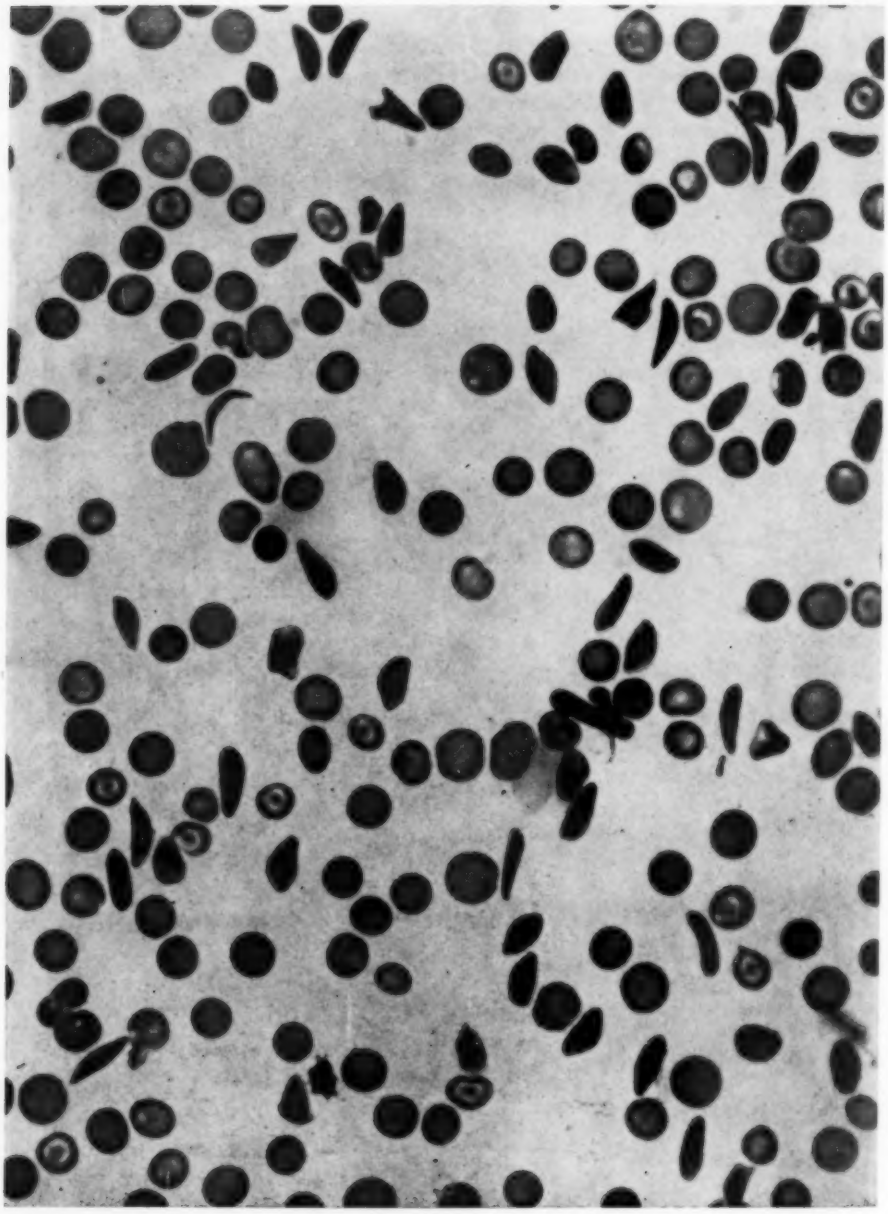

FIG. 2. Typical blood smear obtained during quiescent period, showing abundant sickle cells.

the albumin value, but here also similarly high, relative values for gamma/A were reported by the above authors in aplastic anemia, rheumatic fever, peritonitis and lymphogranuloma.

Prothrombin Studies

Prothrombin times of arterial and venous blood were determined according to the method of Shapiro et al.[30] All determinations were made in

Fig. 3. Biopsy specimen obtained during crisis showing capillary crowded with abnormally shaped erythrocytes including "holly wreath" forms of Sherman and fibrin. Magnification 1,000 ×.

duplicate, and on both whole and 12.5 per cent plasma for each specimen. Controls were run with each determination. As has been described [25-30] a constant relationship was observed between the whole and diluted plasma, and the diluted plasma revealed variations in the prothrombin times in more exaggerated degree than did the whole plasma. There was a total of 44 determinations made on venous blood, 36 of which were accompanied by simultaneous determinations on blood drawn from the radial artery. The average prothrombin time of 14 specimens of whole (undiluted) arterial plasma taken during quiescent periods was 20.1 seconds, the values ranging from 16 to 26 seconds. The average time for the simultaneous 14 venous specimens was 19.3 seconds, the shortest being 16 seconds and the longest 25 seconds. The maximum difference between undiluted arterial and venous blood on any simultaneously drawn specimen was four seconds, and the average difference between these pairs was 1.1 seconds. The corresponding 14 plasma specimens diluted 1:8 with normal isotonic saline averaged 48.1 seconds for arterial blood and 47.8 seconds for venous. The maximum difference between these pairs was six seconds, the average difference being 2.4 seconds. The shortest venous prothrombin time in this group was 42

seconds and the longest 58. The corresponding arterial specimens ranged from 43 to 53 seconds.

It will be seen from these data that there is no constant difference in prothrombin time between arterial and venous blood. It will be seen also that

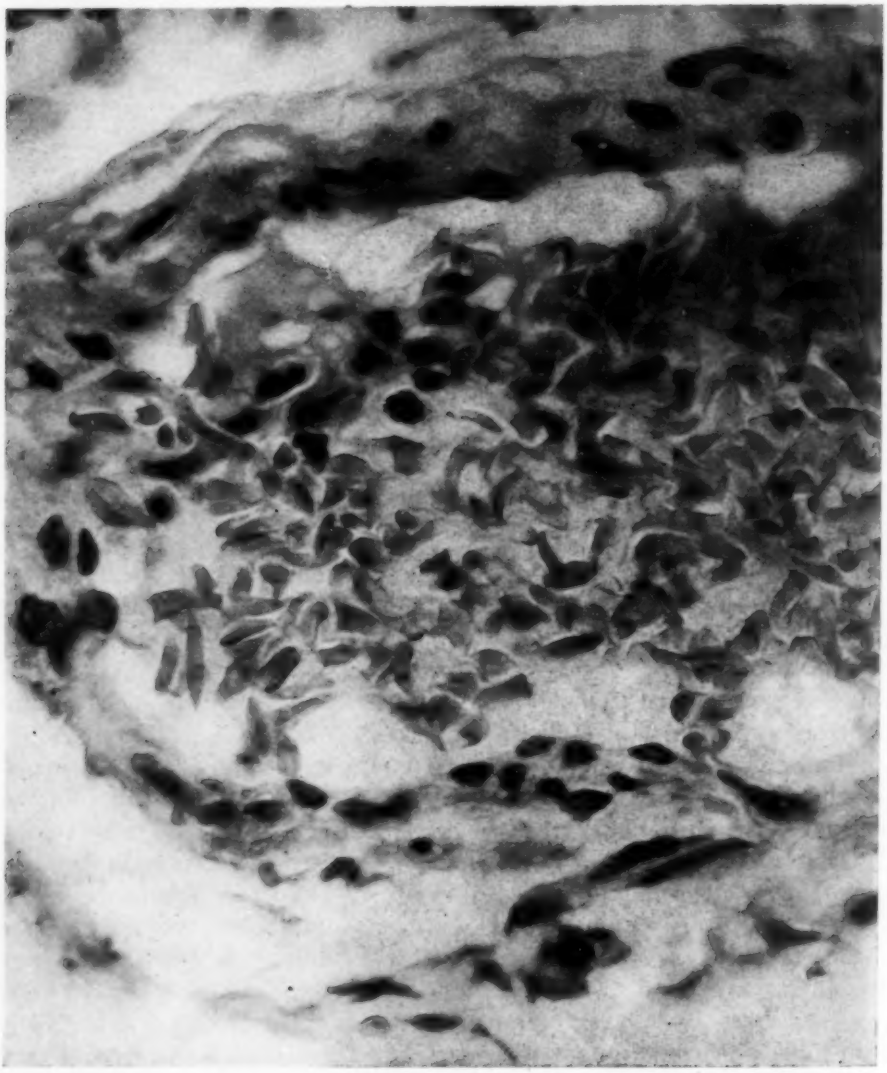

FIG. 4. Biopsy specimen obtained during crisis showing venule occluded by sickle cells. A network of fibrin is present. Magnification 1,000 ×.

during quiescent periods the prothrombin time varied only between the extremes of 16 to 26 seconds for the undiluted specimens and 42 to 58 seconds for the plasma diluted 1 to 8 with normal isotonic saline.

More prolonged prothrombin times appeared on two occasions (omitting consideration of those taken during anticoagulant therapy), and in both cases these prolonged values heralded the approach of sickle cell crises which appeared within the next 24 hours. Thus before one crisis the values for undiluted plasma were elevated to 36 and 33 seconds (arterial and venous) and for diluted specimens to 73 and 66 seconds respectively. The day before another crisis the undiluted prothrombin times were 26 and 28 seconds while the diluted specimens showed times elevated to 62 and 67 seconds. On both these occasions the prothrombin times had returned to slightly below average

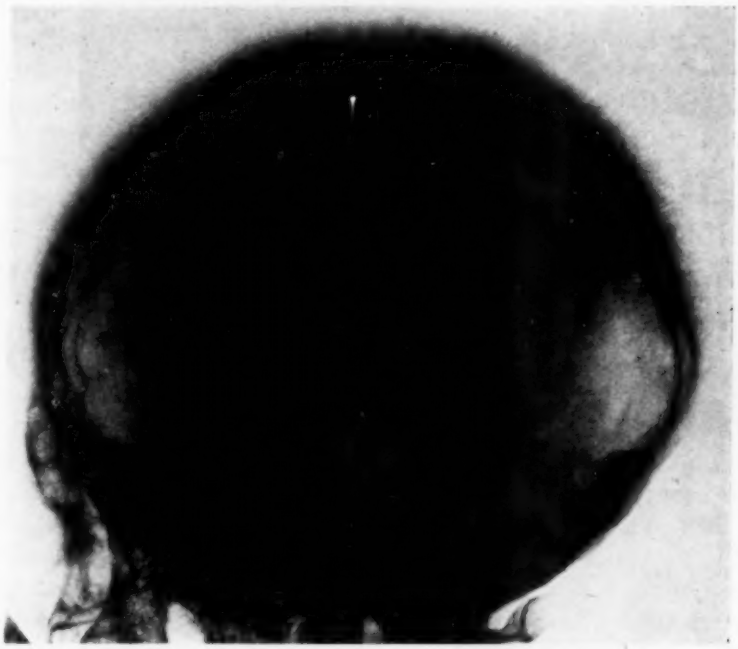

FIG. 5. Radiogram of skull. The tables are thickened and the trabeculae present a "hair on end" arrangement.

readings within 48 hours, that is during the early course of the crisis. On the one other occasion in which we happened to make a prothrombin time estimation during the 24 hour period preceding the onset of a crisis no such prolongation was observed. Nevertheless the results indicate a tendency to prothrombin alterations in connection with the crises, and particularly to an increase in prothrombin time immediately before the onset of a crisis. These observations will be referred to below.

PATHOLOGY

Attempts at treatment were governed by a consideration of the pathology of sickle cell disease. None of the therapeutic efforts used in the case

presented proved themselves to be indisputably valuable, but they helped to throw some light on pathological processes.

Sickling is a property inherent in the red blood cell and not dependent on external factors.[11, 15, 22, 31] It is precipitated in vivo or experimentally by alterations in the ratio of combined to dissociated hemoglobin within the cell.[11, 22, 31] In the body this alteration depends on the oxygen tension of the

FIG. 6. Radiogram of the right hip. The femoral head is irregular. There is flattening and eburnation similar to the picture of caisson disease (aseptic necrosis).

plasma.[22] In the presence of high oxygen tension most of the hemoglobin exists in the combined form as oxyhemoglobin. In this state the red blood cells tend to remain entirely normal in shape and behavior. As the oxygen tension is lowered and the hemoglobin contained in the red blood cell correspondingly dissociated to the reduced form, the cells begin one by one to sickle, until finally (experimentally) 100 per cent of them can be made to assume abnormal form.[22, 31] It appears to be the case that each cell has a

specific threshold, determined by the percentage of its hemoglobin which exists in reduced form, at which it will sickle. Once this threshold is reached sickling is abrupt and almost instantaneous.[22] The process may be reversed by crossing the threshold in the opposite direction. Thus if oxygen is allowed to come into contact with sickled erythrocytes they will immediately revert to the original shape and appear indistinguishable from normal red blood cells.[5, 11, 22, 31] In the circulation sickled forms appear in greatest abundance in the venous circulation, and appear in much fewer numbers in blood simultaneously drawn from arteries, where the oxygen tension is higher.[31] Sickled cells are also found in large numbers in the liver at autopsy [1, 6] and in the spleen at autopsy and at splenectomy.[18] In both these organs the flow of blood may be very slow, and the red blood cells are given the maximum opportunity to discharge their oxygen.[1, 41] We believe that the fibrosis and hemosiderosis characteristic of the spleen in sickle cell disease [1, 3, 6, 13, 40] may be explained by the tendency to stasis of the red blood cell which obtains in that organ. Many of the cells assume sickled form because their hemoglobin becomes dissociated from oxygen, and this factor, together with the stasis, encourages thrombosis of vessels, with infarction and subsequent scarring and contraction.

Before a cell has sickled, or after it has reverted to normal from sickled form, it is essentially indistinguishable from any normal red blood cell. It has an almost jelly-like flexibility and reflects the movements of the fluid medium by gentle undulations and changes in shape. When sickling occurs the cell instantly loses this easy flexibility and appears as fixed and rigid as a crystal of ice as it moves about and abuts against fixed objects.[22] The end to end length of this form may range from two to five or more times the original diameter of the red blood cell, and there are usually long delicate tapering processes projecting from the ends.

It is inconceivable that such a cell could pass through a capillary so small that it just allows passage of a single file of normal erythrocytes. The sickled form is not only the wrong shape to get through terminal capillaries, but it is also too rigid and unyielding.

That jamming and dilatation of capillaries, sinusoids and small blood vessels with interlocking sickled erythrocytes occur has been repeatedly shown to be the case in many types of tissue.[2, 3, 4, 5, 6, 7, 18, 34, 39, 40, 41] The result of this "capillary blockade" is stasis of blood in the capillaries and small blood vessels and subsequent thrombosis. Thromboses of blood vessels represent the most constant pathological finding in sickle cell disease.[3, 5, 6, 7, 18, 32, 40, 41]

No evidence has yet been advanced that the clinical manifestations of the disease are due to anything other than vascular occlusions on the basis of mechanical obstruction and thrombosis. Even if nothing were known of the mechanics of the disease a review of its clinical manifestations suggests vascular occlusion as the fundamental pathologic change. Both pulmonary [6, 18, 40, 41] and cerebral [2, 3, 19, 32, 34, 38, 40] thrombosis and infarction are

common features which have been verified frequently at autopsy. The well known "abdominal crises" of sickle cell disease [1, 19, 32, 36, 38] have not been so thoroughly studied pathologically, but are most probably on a basis of multiple small visceral infarctions, the effects of which are particularly well seen in the small fibrous spleen said to be pathognomonic [13, 34] of the disease. Indolent skin ulcers occur in one-fourth [19] to one-third [13] of the cases. They are extremely chronic and appear usually in the anterior tibial area. Although the etiology of these has not always been recognized,[4] the mechanism clearly appears to depend on capillary and venous occlusions.[13, 19, 32, 41] The ulcers are very similar in their intractable course and in the pathological picture presented [4] to those resulting from varicosities.

Priapism is a not uncommon complication,[6, 8] a fact which also testifies to the blocking of venous spaces.

Progressive renal damage with fixation of the specific gravity as was observed in the case presented is the usual course.[1, 6, 41] This often terminates in uremia [1] if the patient does not first succumb by reason of another aspect of the disease. Pathological studies show this progressive kidney damage to be associated with destruction of the glomeruli by blockade of conglutinated sickled erythrocytes.[1, 40, 41]

Bone and joint pains are among the most common symptoms of sickle cell disease. The pathological changes seen in bones are due to two factors. One is marrow hyperplasia secondary to the severe degree of hemolysis. This is responsible for the ray-like appearance of the trabeculae of the skull as is frequently seen in roentgenograms [6, 7, 20] such as that of the case presented here. The other factor depends again on the essential features of congestion and thrombosis. Autopsied bone specimens show changes characteristic of multiple vascular occlusions.[9] These are: infarction, necrosis, hemorrhage, pigment deposits, hyalinization, fibrosis, abnormal calcification, and new bone formation.[7] The roentgenograms showing eburnation and flattening of the femoral head described here were indistinguishable from the picture sometimes presented by caisson disease, in which the pathologic lesion is known to be due to infarctions caused by multiple air emboli.

The progressive myocardial damage which was seen both by serial electrocardiographic tracings and clinically may have been due to a gradual encroachment of the same process on the margin of safety of the myocardial blood supply. Sickle cell disease is not uncommonly terminated by death in heart failure.[16] In some cases cor pulmonale results with right heart failure predominating. This is secondary to a long standing condition of multiple thromboses of the small pulmonary arteries.[41]

The frequency of pneumonitis in sickle cell disease may be explained by the high frequency of non-fatal or subclinical pulmonary infarcts. In the peripheral circulation vascular blockage and occlusion tend to occur on the venous side of the circulation where oxygen tension is least and the maximum number of erythrocytes is in sickled form.[22, 31] In the pulmonary circulation the oxygen relationships are reversed, arterial occlusions are the rule, and

the incidence of true arterial infarction is higher.[41] The abnormal cells which emerge in increasing numbers from the venous end of the capillaries easily pass through the large veins to the right heart, and out through the large pulmonary arteries, but as they reach smaller pulmonary vessels their tendency to interlace and conglutinate becomes greater and greater. Finally they jam into small vessels and form an impassable meshwork. Stasis then occurs and a pulmonary arterial thrombus forms.

Stasis due to mechanical obstruction appears to be the primary factor in producing all of the lesions of sickle cell disease. As soon as the column of blood becomes static a thrombus forms.[24] The hemolytic manifestations of the disease represent for the most part lysis and resolution of these multiple thrombi.[1] The fever and other constitutional manifestations of the active phase may be accounted for on the basis of the multiple infarctions. The mechanism of the precipitation of hemolytic crises, a subject of considerable speculation,[3, 9, 10] will be discussed below.

Therapeutic Considerations

Since the crises appear to be intimately associated with multiple thromboses it was felt that anticoagulants had a rationale in therapy. If coagulation of the stagnating blood could be prevented long enough to tide the patient over the period of hypersicklemia which presumably initiates a crisis,[3] the severity of the infarctions might be reduced. Mechanical blocking of small blood vessels would still occur, but the accompanying widespread thrombosis might be lessened. Accordingly dicumarol was administered at the first signs of two successive crises. The first of these was "atypical" and the results of therapy difficult to evaluate. At about the start of the other crisis, 500 mg. of dicumarol were administered within 24 hours. The prothrombin time of the whole and diluted (12.5 per cent) plasma was prolonged to a therapeutic level * within 70 hours after the initial dose. However, no significant change was noted in the clinical behavior during this crisis which lasted seven days.

The failure to alter the crisis with dicumarol was thought possibly to be related to the long latent period between the administration of dicumarol and the realization of its anticoagulant effect. An attempt was made to shorten this period by simultaneous administration of 6 gm. of aspirin with the dicumarol, the rationale being that salicylates in large doses prolong prothrombin time [17] and enhance the effect of dicumarol.[26] The prothrombin time showed significant rise within 12 hours, but again the crisis proved to be "atypical" and conclusions could not be drawn.

The last hemolytic crisis in the series was treated with 400 mg. of dicumarol in four divided doses during the first day. During the first and second days of the crisis the patient also received 300 mg. of heparin in frequent intravenous doses. The coagulation time was determined every

* The whole plasma prothrombin time was prolonged to about double normal and the diluted (12.5 per cent) plasma prothrombin time to between twice and three times normal.

three or four hours and was maintained between 15 and 35 minutes during heparin therapy. By the time the heparinization was stopped the prothrombin time had risen by reason of the dicumarol effect to 27 (venous) and 26 (arterial) seconds, and after an additional 400 mg. of dicumarol marked prothrombinopenia was induced.

Despite this vigorous anticoagulant therapy there was no amelioration of symptoms. This crisis was, in fact, the severest to date. There was massive hemolysis, the patient became grossly jaundiced, congestive heart failure and pulmonary edema developed, and the immediate prognosis for a time looked very grave despite intravenous digitalization and oxygen therapy. It is to be noted, however, that 14 hours elapsed between the sharp painful onset of the crisis and the first dose of heparin.

Comment

If anticoagulants are of any use at all it appears that they must be in effect promptly, immediately as the crisis commences. Typical crises begin abruptly, a fact which suggests that the sickled cells precipitate out in a massive capillary blockade more or less simultaneously. If this is the case then the major part of the vascular thromboses associated with a hemolytic crisis must occur within a few hours of its sudden onset. Anticoagulants would have to be in effect extremely early to affect the course of a crisis.

The supposition that most of the vascular occlusions responsible for the crisis occur very early is not incompatible with its clinical course. The several days characterized by pain, fever and other constitutional symptoms following the abrupt onset of a crisis represent simply a period during which the multiple infarctions are resolved and the circulation is reëstablished. The hemolytic manifestations represent resolution of the thrombi, and also mechanical breaking up of the brittle sickled cells when forced into capillaries too small to accommodate them.

Mechanism of Hemolytic Crises

It is generally agreed that the pathology of sickle cell disease is associated with multiple vascular occlusions as detailed above.[1, 3, 5, 6, 7, 13, 19, 22, 32, 39, 41] However, there is no such agreement in explaining the increase in circulating sickled erythrocytes which is thought to be responsible for the multiple occlusions that precipitate a crisis. Hypotheses, such as that crises are caused by sudden hypersicklemia due to intercurrent disease [3, 9] have no foundation in clinical observation.

Our explanation for the occurrence of hemolytic crises involves the hypothesis that there is an inevitable accumulation of circulating sickled cells in the interval between crises, due to an increasing tendency of the erythrocytes to sickle as they become older. The concentration of the sickled form eventually becomes so high that, possibly owing to alterations in the coagulating mechanism of the blood, they suddenly precipitate out in a more or less

simultaneous capillary blockade, initiating a new crisis. By this capillary blockade far greater proportions of sickled red blood cells are destroyed than of those which are still normal in shape. Thus at the end of a crisis there are in circulation relatively few erythrocytes in the sickled form. The abnormal form, however, gradually increases in the circulation during the 10 to 30 days between crises until it reaches a certain critical limit, at which time the massive precipitation of elongated erythrocytes again occurs. The trigger mechanism which sets off this precipitation appears most probably to be a change involving a temporary increase in blood coagulability, and will be discussed presently. During the intercritical period there is by no means a cessation of hemolytic activity. Great numbers of the long brittle erythrocytes are still broken up by the trauma of capillary passage, as reflected in the sustained hyperbilirubinemia. There may also be a small degree of capillary thrombosis contributing to the sustained low-grade hemolysis. There is, however, a relative equilibrium between hemolytic and blood regenerative factors, a condition favorable to the latter, as the level of red elements in the blood rapidly builds up during this relatively quiescent period.

It has been our observation that normoblasts, reticulocytes, and red cells showing polychromatophilia or other evidences of immaturity are very rarely seen in sickled form. Although sickled normoblasts have been reported,[7, 36] it is commonly noted that none of the younger forms of the red blood cell sickle readily.[5, 7, 36, 40] Sickling, therefore, is partly a function of age, at least to the extent that immature erythrocytes are less susceptible to the tendency than are the mature cells. In other words the sickling threshold (as determined by the oxygen concentration of the blood) decreases as the cell ages. Presumably the threshold is first reached under the conditions prevailing in venous blood so that the cell sickles only as it emerges from the venous end of the capillary, and resumes normal shape upon reoxygenation in the lungs. If the decrease in sickling threshold is progressive the change will thereafter occur more and more toward the arterial end of the capillary until finally the threshold passes below the oxygen tension of arterial blood. At this point the cell becomes permanently sickled as long as it remains in the body.

Immediately after the massive destruction of erythrocytes which accompanies a crisis, the circulating blood cells tend to be young, with immature forms constituting a large fraction of the total number. As the red cells mature during the quiescent interval they become increasingly more susceptible to the sickling tendency, with a resulting gradually increasing accumulation of sickled forms between the crises.

This accumulation of sickled forms might be prevented or minimized if the red blood cells were more easily destroyed while in sickled than in normal form. However, no evidence has been advanced to suggest that sickling per se shortens the life of the red blood cell. Sydenstricker,[35] using the wet smear technic, recovered sickle cells from a normal subject 23 days after transfusion with the blood of a patient with sickle cell disease, thus proving

their longevity for at least this period. Although it cannot be proved that these cells were all circulating in sickled form, the nature of the sickled cell suggests in any case that it is probably more resistant to the phagocytic action of the reticulo-endothelial system than are normal erythrocytes. The erythrocyte in sickled form has been demonstrated to have a decreased resistance to physical trauma,[5] as might be predicted from its observed rigid and inflexible character. Its resistance to osmotic trauma, on the other hand, is markedly increased over that of normally shaped erythrocytes, as is noted in fragility tests and in our observations that the sickled cell never crenates. Therefore, although the erythrocyte in sickled form is more easily broken up by the trauma of capillary passage, its resistance to chemical and osmotic traumata, which are presumably the destructive weapons of the reticulo-endothelial system, may be abnormally great. Normal erythrocytes lose their resistance to the destructive action of histiocytes as they become old, and when senile are finally phagocytized. The sickled erythrocyte presumably becomes all the more unalterably sickled as it approaches senility, and may thus increase rather than lose its resistance to phagocytosis with age. Such an hypothesis is entirely compatible with the common observation at autopsy that there is a high degree of phagocytosis of sickled cells throughout the reticulo-endothelial system, an observation which has frequently been urged as evidence for the hypothesis that sickled cells are more easily destroyed than normal cells.[1, 6] This observation may be used equally well as evidence for our diametrically opposite hypothesis. The erythrocytes seen in the Kupffer cells and other histiocytes may represent whole sickled cells, broken particles of previously traumatized sickled cells, or cells which were ingested while normal in shape and which sickled immediately thereafter. In any of these three cases their prolonged resistance to destruction by the histiocytes which have engulfed them may well explain the high degree of phagocytosis and hemosiderosis which persists and is found at autopsy.

During a hemolytic crisis it is the mature erythrocytes or those that sickle most readily which are chiefly involved in the massive mechanical and thrombotic destruction of red blood cells. The immature forms tend to retain their normal shape. Some of these must become caught in the meshworks of conglutinated sickled cells, but for the most part those red cells which have not sickled will tend to escape hemolysis because they offer no obstruction in capillary passage. As a result the blood literally becomes "rejuvenated" by a crisis. The young red blood cells which thus escape destruction may well become the sickled forms which develop during the next intercritical period and which are in turn responsible for the next crisis.

It might still be argued that the initiation of crises is associated with the development of sudden hypersicklemia. During a crisis great numbers of young red blood cells are thrown into the circulation and there is marked evidence of marrow stimulation. The reticulocyte count rises, large numbers of normoblasts appear, and the leukocyte series may even show a marked myeloblastosis. If it were supposed that sickling occurs at a uniform age

in all of the red blood cells, then there would be a fairly abrupt rise in the rate of sickling at a certain definite interval after the sudden rise in reticulocytosis. However, the evidence does not support such a supposition. Furthermore the initiation of a crisis is so dramatically acute that it could hardly be due to such a gradual process.

The trigger mechanism which sets off the massive precipitation of sickled erythrocytes and blockade of capillaries seems most probably to be an altered state of blood coagulability. As has been discussed, the features most characteristic of the pathologic lesions of sickle cell disease are mechanical obstruction of capillaries and vascular thromboses. These two factors are closely interrelated. Once stasis of blood occurs for whatever cause, thrombosis necessarily supervenes.[24] Furthermore a sudden increase in blood coagulability must in turn enhance the tendency to capillary blockade, as vessels which were only partly occluded thereby become thrombosed. Although a small proportion of the circulating sickled cells is being continually broken up and lysed, the rate of their destruction is apparently not great enough to establish an equilibrium. The result is a progressive reaccumulation of the sickled form in the circulation. Until an equilibrium is reached between the maturing-sickling process on the one hand and the breaking up of the sickled forms on the other, the circulation must progress toward "saturation" with sickled forms, in the sense that any further increase becomes incompatible with free circulation. Then the abnormal erythrocytes will begin to precipitate out into the capillaries at the same rate that they sickle. If it should happen, just at this stage, that an excess of blood coagulants were suddenly thrown into the circulation, the sicklemia would thereby be changed from a "saturated" to a "supersaturated" condition, and precipitation would take place in a massive capillary blockade favored by the increased tendency to capillary thrombosis.

Local thromboses have been found to be reflected in a systemic response in the order of increased coagulability of the blood.[30a] Especially is this true when thrombosis is by coagulation (fibrinous) as opposed to simple agglutination. Our biopsy picture of capillary blockade reveals a fibrin network.

It is shown by clinical and pathological studies that the coagulability of the blood does increase in association with the crises. Thrombosis of large vessels such as the cerebral arteries,[2, 3] pulmonary arteries [41] and large abdominal vessels is one of the constant manifestations of sickle cell disease in its active phase. These thromboses are obviously not due to mechanical obstruction, as occurs in blood vessels of very narrow lumen, but reflect, instead, a true thrombotic tendency of the blood. Thromboses of this sort are not reported as occurring during the quiescent phase of the disease.

The mechanism of the rather abrupt change in blood coagulability which accompanies the crises may be explained by a progressive increase in the degree of capillary obstruction associated with the accumulation of sickled cells in the circulation. A thrombus forms in each of the tiny columns of blood as

soon as it becomes static,[24] with the result that small amounts of coagulating substances such as free thrombin and thromboplastin are released into the circulation.* Under normal circumstances these substances are disposed of and probably cause no increase in total concentration of coagulating substances. However, when the degree of capillary blockade and thrombosis becomes so extensive and generalized that the red cells begin to precipitate into the capillaries as fast as they sickle, the concentration of free coagulants may actually be increased in the blood as a whole. However slight this excess of circulating coagulants may be, it will necessarily encourage the tendency to thrombosis of imperfectly occluded capillaries, with the result that both the coagulability of the blood and the tendency to capillary obstruction and occlusion begin to rise sharply. Once the rate of thrombosis rises the thrombotic tendency of the blood is further accelerated, and the crisis rapidly gathers momentum.

The curve of arterial and venous prothrombin times is of interest in this regard. There is a tendency for the level of prothrombin to become significantly reduced immediately as the crisis becomes clinically perceptible and then to increase about 24 hours after the onset. A clear explanation for these precritical prothrombin time prolongations is lacking, but it is interesting to speculate that they may be the result of excessive utilization coincident to the diffuse thrombosis, the prothrombin elaborating mechanism being unable to respond adequately for about 24 hours when the level commences to approximate normal. On the other hand, it may represent a protective and compensatory mechanism whereby the organism attempts to inhibit coagulation in the face of spreading thrombosis. Similar phenomena have been detected clinically coincidentally with hypercoagulability of the blood in other thrombotic conditions.[29, 30a]

Comment

The ultimate disturbance of sickle cell disease is not to be found in an analysis of its ostensible pathology, but rather in a fundamental abnormality of erythropoiesis. The asymptomatic sickle cell trait was exhibited by the father of the patient here presented. It differs from the clinical disease only in a higher threshold of sickling of the erythrocytes.[31] In both conditions all of the erythrocytes are affected, in that they can all be made to assume the abnormal form.[22]

Summary

In sickle cell disease there occur hemolytic crises of varying severity separated by periods of relative quiescence. Accompanying the crises are fever and disseminated pains produced by multiple infarctions which may be visceral as well as skeletal. Hemolytic aspects representing resolution of thrombi and disintegration of the sickled cells are prominent.

* The hyperfibrinogenemia disclosed in the electrophoretic patterns might play an important rôle in the mechanism.

The pathology of sickle cell disease is determined by the diffuse infarcts, which in turn stem from the abnormal shape and other physical characteristics of the sickled erythrocyte.

During the time a susceptible cell retains the normal shape it is indistinguishable in behavior from normal erythrocytes. The act of sickling, however, renders it elongated and rigid, making capillary passage difficult. As the sickled forms gain prominence in the blood stream they eventually form a mechanical impaction delaying the capillary flow. As a result of the static blood flow thrombosis takes place. This constitutes the fundamental pathologic lesion of sickle cell disease.

All erythrocytes of a subject with the asymptomatic sickle cell trait are capable of assuming the abnormal form and differ from those of persons who exhibit the crises only in that they (the former) possess a higher threshold of sickling.

Susceptible red cells exhibit increased tendency to sickling as they mature. Evidence is lacking that sickling affects the longevity of an erythrocyte, hence the abnormal form tends to increase progressively during the quiescent periods until mechanical obstruction and thrombosis of capillaries occur. With each thrombosis there are liberated into the circulation certain coagulating bodies (thrombin, thromboplastin) which further enhance thrombosis and accelerate the precipitation out of the circulation of sickled red cells. A self perpetuating sickle cell "crisis" is thereby inaugurated which gains momentum until the major part of the sickled cells are destroyed and the blood is again "rejuvenated" by release into the circulation of immature normally shaped cells.

The sudden liberation of coagulating bodies into the circulation accounts for thrombosis of larger blood vessels also.

Anticoagulant therapy appears to be inadequate to prevent a crisis. If in effect at the abrupt onset of a crisis anticoagulants might postpone the thrombotic tendency of the blood; they could not, however, prevent the increased tendency of the cells to sickle as they grow older, which tendency leads inevitably to the vascular occlusions.

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THE DIAGNOSIS OF BERIBERI HEART DISEASE*

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ALTHOUGH we have made great progress in our understanding of deficiency diseases and similar progress in cardiology, not much seems to be known about beriberi heart disease, if we can judge by American publications. To elaborate this idea the following statements can be made. The diagnosis of thiamin deficiency, i.e., American beriberi, can be made with reasonable certainty, as shown by the studies of Aring and Spies at Birmingham [1] and by others. Thiamin is a specific cure for the reversible manifestations of the disease and is a safe and easily administered remedy. Soma Weiss in 1937 [2] showed the similarity of oriental beriberi to that seen in this country. He found 35 cases in the Boston City Hospital in two years and said "beriberi was of regular occurrence," i.e., not rare. Later, in 1940 when crystalline vitamin B was available, he showed that occidental beriberi was curable by that drug.[3]

Williams and others at Rochester, Minnesota, have demonstrated that volunteers on deficient diets may show symptoms of cardiac insufficiency as well as electrocardiographic changes.[4]

Meanwhile, recently revised cardiology texts give beriberi little mention and current literature gives perhaps less. A number of factors other than conservatism may account for this apparent reluctance to diagnose beriberi heart disease.

The first factor is that there is no distinctive pathological picture that can be recognized at present.

Secondly, the pathogenesis, especially in as far as this can be deduced from symptoms and signs, is not understood. This latter greatly concerns the cardiologist who comprehends the circulation in dynamic terms.

Thirdly, the concept of the disease is dominated by descriptions of the malady as seen in the Orient at a time when the pathologic lesions, the pathogenesis, and even the treatment were not understood.

The present state of our knowledge as to pathology and pathogenesis of beriberi heart disease is not much further advanced, but our knowledge of heart disease is. In particular, many conditions which might formerly be confused with beriberi are better understood. This is true of hypertension, scurvy, rickets, and the effects of numerous intoxications that were traditionally associated with the clinical diagnosis of myocarditis or the electrocardiographic interpretation of myocardial damage.

While we have disposed of a variety of doubtful causes and a number of idiopathic forms of heart disease, our information about deficiency states

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has increased greatly. Now, too, a therapeutic test can be employed with certainty in many cases. This writer believes, as did Soma Weiss, that the disease is not rare in general hospitals where other deficiency diseases occur, and that it can be recognized and even cured at times, and further that beriberi may complicate chronic heart disease of other etiology.

On the Medical Wards of the Cincinnati General Hospital, beriberi heart disease has been diagnosed 10 times in a period of four years by the combined efforts of the Departments of Cardiology, Neurology and Nutrition.

The Department of Cardiology has provided the experience necessary to discover or rule out known forms of heart disease other than beriberi. The Department of Neurology has described methods of clinical examination which reveal minimal signs of peripheral neuritis and has established American beriberi as a clinical entity. The Department of Nutrition has prescribed methods of recognizing nutritional neuritis and estimating the nutritional status of individual patients.

TABLE I

1. Enlarged heart with normal rhythm (sino-auricular).
2. Dependent edema.
3. Elevated venous pressure.
4. Peripheral neuritis or pellagra.
5. Non-specific changes in electrocardiogram.
6. No other cause evident.
7. Gross deficiency of diet for three months or more.
8. Improvement and reduction of heart size after specific treatment, or autopsy findings consistent with beriberi.

A tabulated scheme showing the criteria for diagnosis as finally agreed upon is presented herewith (table 1) and for comparison (table 2) the usual or traditional criteria as described by Wenckebach [5] for oriental beriberi and as emphasized by Soma Weiss. When the traditional criteria only are followed in the diagnostic study of unusual heart disease, very few patients can be diagnosed as beriberi. When the meager case material in current literature is inspected for these criteria, few cases conform. For that reason other criteria based on more recent concepts of nutritional disease and of heart disease have been used at the Cincinnati General Hospital.

We think there is a need for the early recognition and the selection of mild cases which may advantageously be subjected to more rigid and prolonged nutritional control than we are now practicing. There is also need for recognition of the mild stages which may complicate other forms of heart disease. To facilitate this recognition is the purpose of this paper.

The accepted criteria for the diagnosis of beriberi heart disease at the Cincinnati General Hospital are:

Enlargement of the heart is demonstrated in every instance by the measurements found in a roentgenogram made at 72 inches. If the greatest cardiac diameter exceeds one-half the chest diameter, the heart is regarded as enlarged. This method of estimating heart size is not above criticism, but the method is adequate to demonstrate the subsequent reduction that

TABLE II

Beriberi Heart Disease, Incidence of Traditional Signs, Ten Cases at Cincinnati General Hospital, 1940 to 1944

Name	Age	Sex	Abnormally Rapid* Circulation	Prominent Rt. Heart	"Pistol Shot"	Gallop Rhythm	Syncope or Shock	Critical Improvement After Specific Treatment	Comment
H. R.	41	M	40 sec. 0	0	0	+	+	0	Died, autopsy
H. S.	46	M	?	0	0	0	+	0	Died, autopsy
F. R.	33	M	21 sec. 0	+	0	+	+	0	
T. B.	53	M	14 sec. +	+	0	0	0	0	
J. K.	47	M	13 sec. +	+	+	0	0	0	
M. D.	56	F	?	0	0	0	0	+	
J. D.	55	M	13 sec. +	0	0	0	0	0	
G. B.	67	M	52 sec. 0	+	0	+	+	0	Died, no autopsy
J. B.	39	M	13 sec. +	?	?	0	+	0	Died, no autopsy
J. B.	53	M	11 sec. +	?	++	+	0	0	No neuritis

* Decholin method for "circulation time."

follows recovery. Due regard to the possibility of hydrops of the pericardium can usually eliminate pericardial effusion as the sole cause for increased diameters.

The term "normal rhythm" as used means a normal origin and propagation of the heart beat, even if gallop rhythm is present.

Venous pressures were done directly, and 10 cm. of water regarded as the upper limit of normal. It is assumed that in some of our patients in severe shock and with systolic arterial pressures below 100 a venous pressure of 10 cm. may be a high venous pressure.

I consider the diagnosis of neuritis the most important point in determining that the patient is deficient in his store of vitamin B_1, and refer to the article of Dr. Aring,[1] Neurologist in the Cincinnati General Hospital, for criteria of diagnosis. When there is much edema, signs of neuritis may be obscured, and they may be demonstrable only after edema subsides. Since neuritis of the lower extremities does not clear rapidly even when treated, it is expected that some residual signs will remain in every case. It is not believed that dependent edema can cause or simulate neuritis.

The importance of finding signs of pellagra in a person with heart disease arises from our concept of pellagra as a multiple deficiency. We find many patients who have been diagnosed as pellagrous who later show neuritis also. Therefore, in assessing the state of nutrition as an index of the store of vitamin B_1, a diagnosis of pellagra is next in importance to the diagnosis of beriberi.

The electrocardiographic changes are always slight and have been mentioned by many cardiologists, viz., "small complexes, negative T-waves in Lead 1, and slight aberration of the ventricular complexes" (White).

As to the sixth criterion it is patent that the less one looks for the causes of heart disease the less will be "evident." For that reason it is our custom to defer to the cardiologists whose special technics in recent decades have eliminated as etiologic agents in the causation of heart disease such factors as the use of aspirin, athletic heart, beer drinking, lead, tea, coffee, and perhaps even tobacco.

In estimating gross deficiency of diet we rely on the members of the Department of Dietetics, who, by a method of diet survey, are able to report as "good, fair or poor" the qualities of the recent diet. The minimum duration of such a diet was arbitrarily set at three months. The experimental production of human beriberi by Williams and others [4] has aided in this arbitrary choice.

The specific treatment generally used was 20 to 50 mg. of thiamin intravenously given daily for a space of two weeks. This is known to be an excessive dose, but no harm has come from it. We have usually withheld this specific treatment until the effects of bed rest could be observed. During this period of control and study digitalis and diuretics have occasionally been given. Usually beriberi heart disease is not improved by either, but the result of such treatment is not sufficient to demonstrate the nature of the disease. There is now no certain therapeutic test which will prove the diagnosis of beriberi or exclude it. We regard improvement with reduction of heart size as very suggestive because there are so few diseases of the heart in which prompt and lasting reduction occurs during the ordinary treatment in the hospital. We do not consider the failure to improve with thiamin treatment as proof that beriberi is to be excluded. Our case, H. R., is an example.

As to the diagnosis at autopsy our colleague, Dr. Austin, follows the criteria of the New York Heart Association as published in 1939; viz., "Microscopically the myocardium may show no changes or the myocardial fibers may present various degrees of hydropic degeneration. Longitudinal and cross-striations may remain. Intercellular edema, congestion, hemorrhage and swelling of the connective tissue may be present. These changes, however, are not specific."

The differential diagnosis must exclude Fiedler's myocarditis or isolated myocarditis. In this we follow the criteria as published by Karsner.[6] Separation of beriberi from idiopathic hypertrophy with mural thrombosis and

from congenital idiopathic hypertrophy may be impossible with the present criteria for the clinical recognition of those diseases. A recent discussion of this problem by William Dock [7] and the report by Kugel and Stoloff [8] show the difficulty that develops as nutritional study is added to the usual methods. The essence of that discussion and the report on congenital idiopathic hypertrophy is that both these conditions may be due to deficiency disease.

When the 10 patients at the Cincinnati General Hospital diagnosed by the criteria in table 1 are examined for the traditional signs of beriberi heart disease, the findings are as summarized in table 2. It can be seen that rapid circulation was found in five of eight patients tested by the decholin method. Slow circulation was found three times. In no instance was the time abnormally short, but the time was short in view of the degree and duration of congestive failure when specific treatment was started.

Prominent right heart was described four times by the clinicians who noted abnormal pulsation over the pulmonary conus and accentuation of the pulmonary closure. There was no electrocardiographic, radiographic or necropsy evidence of right ventricle hypertrophy.

"Pistol shot" sound was recorded twice and was not tested once. In both patients a large pulse pressure was found when "pistol shot" was recorded. In one instance loud "pistol shot" was heard in each dorsalis pedis artery (J.B. in table 2). In all the others the pulse and blood pressure were not suggestive of rapid circulation.

These three traditional signs of accelerated blood flow have been emphasized in the writing of Wenckebach and in his explanation of causes.[9] Porter and Downs [10] applied modern physiologic methods to a study of these three signs in patients at the Brigham Hospital. The latter were unable to conclude that such circulatory faults were important as a cause nor even essential to the diagnosis. Our experience is in harmony with them and not with that of White, who seems to regard "vasodilatation and rapid blood flow as a late sign or occurring only in advanced cases." We have seen this sign in three patients known to be chronic alcoholics at a time when no sign of failure could be shown and who are not, therefore, included in this series. In these three patients rapid heart and rapid blood flow were critically changed by treatment but they did not show heart disease otherwise. One such patient was readmitted eight years later with failure (J. D. in table 2). One half of our patients showed very low blood pressure or attacks of syncope or both. The high incidence of such signs of danger has made us reluctant to make a prolonged control study for purposes of diagnosis and to explore the nature of the disordered circulation when such signs are present.

When our proposed criteria and the traditional criteria are considered as a whole, it appears that beriberi heart disease is both a myocardial disorder and a disease of the nervous system, and comprises no rigid syndrome. In this we are entirely in harmony with the last published views of Soma Weiss,[11] but we think that undue emphasis on the traditional criteria will

exclude many cases from recognition and treatment. When such case material as can be found in recent literature is tested by these traditional criteria very few cases conform. The case material studied by Jolliffe and Goodhart [12] with regard to the cardiovascular complications of chronic alcoholism also did not show acceleration of the circulation or enlargement of the right heart as a predominating feature or a late sign.

Summary

We concur in the opinion of the late Soma Weiss that beriberi heart disease is both a disturbance of the myocardium and the nervous system, and that it is not a rigid syndrome nor a rare one. The following criteria are proposed.

Beriberi heart disease may be diagnosed when there is found present:

1. Enlarged heart with normal (sino-auricular) rhythm.
2. Dependent edema.
3. Elevated venous pressure.
4. Peripheral neuritis or pellagra.
5. Non-specific changes in the electrocardiogram.
6. No other cause evident.
7. Gross deficiency of diet for three months or more.
8. Improvement and reduction of heart size after specific treatment or autopsy findings consistent with beriberi.

Rapid peripheral circulation and prominence of the right heart are not often found in the patients recently diagnosed as beriberi heart disease in this country, even though such signs have been regarded as important diagnostic criteria. Suspected and early cases should be subjected to the strict therapeutic control and extensive physiologic study necessary to demonstrate the true nature of the disease. Late cases, especially those showing low blood pressure and syncope, are not suited to such study.

Beriberi heart disease may be found as a complication of other forms of heart disease.

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THE TREATMENT OF BRONCHIECTASIS WITH CHEMOTHERAPY AND ALLERGY MANAGEMENT *

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This study is an evaluation by follow-up examination and questionnaires of sulfonamide therapy and allergy management in the treatment of 75 cases of bronchiectasis. In 13 cases operation was indicated but had been refused or postponed by the patient. The remainder of the cases were considered non-surgical because of minimal or advanced disease, age, general condition, or because benefits from allergy management could be anticipated. The period of observation varied from four months to five years; the majority were observed for two years at least. Consequently, the report is preliminary.

Bronchiectasis was first described by Laennec [1] in 1819, but not until iodized oil as a radio-opaque medium was introduced by Sicard and Forestier [2] in 1922 did the disease become more widely recognized.

Lobectomy has proved to be the only permanently curative procedure. Although improved surgical technic, cutting mortality from 60 per cent prior to 1929 to less than 3 per cent,[3, 4, 5] has extended radical and curative procedures to less advanced cases, operation is frequently contraindicated because of age, extent of involvement, minimal pathologic lesions, or refusal of operation. For these patients palliative measures have proved of little or no value.

The most obvious feature of bronchiectasis is considered to be inflammation of the tertiary bronchial tubes and adjacent pulmonary parenchyma caused by bacterial infection, which may be secondary to many unrelated conditions of the respiratory tract. That obstruction of a bronchus in addition to bacterial infection is necessary in the production of bronchiectasis has been repeatedly demonstrated experimentally. However, bronchiectasis does not develop from bronchial obstruction in the absence of pulmonary infection. Lisa and Rosenblatt [6] in studying 110 autopsies found that the so-called bronchial dilatation was actually an epithelialized cavity communicating with the bronchus and that these cavities resulted from inflammatory destruction of the bronchial wall. As they pointed out, bronchial obstruction is not a mechanical factor in producing bronchial dilatation, but rather it promotes infection in the bronchus.

Watson and Kibler [7] suggested that primary allergic bronchitis may be an etiologic factor in a large percentage of cases of bronchiectasis. They con-

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tended that allergic swelling of the mucosa and outpouring of tenacious secretions combined with bacterial infection and poor drainage seemed adequate cause for producing atelectasis and, in a variable time, bronchiectasis. Although Watson and Kibler emphasized the importance of atelectasis, the really significant factor seems to be promotion of infection by obstruction and atelectasis and by impairment of function of smaller bronchi and bronchioles such as occurs in bronchial asthma and perennial allergic bronchitis. Although the cough reflex is initiated by exudate or foreign material in the larger bronchi, the smaller branches of the bronchial tree depend upon the action of cilia and musculature for expulsion of foreign material. The impairment of this process in bronchial asthma and allergic bronchitis increases susceptibility to pulmonary infection. Undiagnosed bronchostenosis as a sequel to pneumonia, bronchitis, whooping cough, influenza, or bronchial asthma may be an etiologic factor in the production of bronchiectasis more frequently than is realized. Perennial allergic bronchitis and bronchial asthma are nearly always accompanied by perennial allergic rhinitis which frequently predisposes to sinus infection. There is some disagreement about sinusitis as an etiologic factor in bronchiectasis. However, chronic drainage of septic material from the sinuses may lead to development of bronchiectasis, particularly in persons having bronchial asthma or allergic bronchitis with obstruction and impaired function of the smaller bronchi and bronchioles. Moreover, bacterial sensitivity no doubt plays a large rôle in the relation of allergy and bronchiectasis.

Of 190 consecutive cases of bronchiectasis seen over a five year period 48 per cent had a major allergy of the respiratory tract. In comparison in 15 of the 75 cases in this series the only predisposing factor was allergy of the respiratory tract. In about half of the group with a history of respiratory infection allergy was considered to be a complicating factor. Frequently the symptoms for a number of years after the initial infection were obviously those of allergic bronchitis or sometimes bronchial asthma. In 31 cases sinusitis was found on the initial examination, or there was a history of pus having been found on irrigation of the sinuses; 28 of these had associated allergy of the respiratory tract.

Therefore, since bacterial infection is the fundamental factor in the pathogenesis and symptomatology of bronchiectasis and since allergy is an associated or predisposing factor in such a large percentage of cases, the most logical palliative treatment would include sulfonamide drugs and allergy management. In the future less toxic and more potent drugs will probably replace the sulfonamides. Penicillin should be considered in this group of newer drugs and used in the treatment of bronchiectasis.

Little appears in the literature concerning sulfonamide drugs or allergy management in the treatment of bronchiectasis. Watson and Kibler [7] were the first to point out an allergic factor in the etiology and to suggest allergy management in the prevention and treatment. In 1941 Van Ordstrand [8] suggested the use of sulfonamides. Recently Norris [9] published results in 10

cases in which intratracheal and intrabronchial instillations of 5 per cent aqueous suspension of sulfathiazole combined with bronchoscopy resulted in definite reduction in daily sputum. It was found that the concentration of sulfadiazine in bronchial secretions during oral administration was approximately 60 per cent of the blood level and was not materially affected by the extent of bronchial disease or the amount of expectoration. Harris [10] also used intrabronchial insufflations of sulfathiazole in a few cases with good results. Albritten and Flick [11] used sulfanilamide in partial and total resections of the lung and believed that the incidence of pleural infection was less than when sulfanilamide was not used preliminary to operation. Graham,[12] however, in a series of 23 cases and controls did not find sulfonamides of any help.

Material of Study

Thirty of the 75 patients were men and 45 were women. When they first presented themselves for treatment, their ages ranged from 4 to 76. The majority were over 30 years of age (table 1). The age at the onset of symptoms varied from infancy to 69 years (table 2).

Table I

Age When Patient First Presented Himself for Treatment

Age	Patients	Per Cent
0– 9	3	4
10–19	8	11
20–29	8	11
30–39	20	27
40–49	20	27
50–59	11	14
60–69	4	5
70–79	1	1

Table II

Age at Onset

Age	Patients	Per Cent
0– 9	28	37.33
10–19	6	9.0
20–29	12	16.0
30–39	11	14.23
40–49	12	16.0
50–59	4	5.33
60–69	2	2.66

The duration of symptoms ranged from two months to 45 years. Fifty-five per cent had symptoms for 10 or more years (table 3).

Table III

Duration of Symptoms

Duration in Years	Number of Patients
Less than 1 yr.	6 (8%)
1– 4	18 (24%)
5– 9	10 (13%)
10–19	20 (27%)
20–45	21 (28%)

The disease varied in severity from minimal to far advanced. All 75 patients gave a history of cough with expectoration, which was purulent in all but two cases. The amount of expectoration each 24 hours varied from ½ ounce to 32 ounces. Fifty-five patients expectorated more than two ounces each 24 hours. There was history of frank hemoptysis in 16. Three patients had cor pulmonale. When first seen 26 had fever, usually low grade. Thirty had dyspnea, and 17 had lost weight.

On initial examination of the chest 67 patients had findings typical of bronchiectasis. Stereoscopic roentgenograms of the chest were highly suggestive of bronchiectasis in 35; in 40 they were questionable or negative. Lipiodol bronchography established the diagnosis in 55 cases. Bronchoscopy was done in nearly all of these to rule out any obstructive lesion; in three cases in which the bronchograms were negative or not satisfactory localization was determined by detecting the orifice from which the exudate originated. The diagnosis was established in the remainder of the cases by the history, physical examination, absence of tubercle bacilli and fungi in the sputum, and stereoscopic and plain films of the chest.

TABLE IV

Localization of Pathologic Process in 57 Cases Determined by Bronchograms or Bronchoscopy

Unilateral		31
	Right upper lobe	1
	Right middle lobe	2
	Right lower lobe	10
	Left upper lobe	0
	Left lower lobe or left lower lobe and lingula	17
	Left upper lobe and left lower lobe	1
Bilateral		26
	Lower lobes	22
	Lower and middle lobes	4

TABLE V

Type of Bronchial Dilatation

Fusiform	31
Saccular	17
Fusiform and saccular	6

Bacteriologic studies of bronchoscopic aspirations in 41 patients revealed in order of frequency nonhemolytic streptococcus, *Streptococcus viridans,* hemolytic streptococcus, pneumococcus, fusiform bacillus and spirochetes, fusiform bacillus and streptococcus, *Neisseria catarrhalis,* streptococcus, and *Staphylococcus albus,* and *Haemophilus influenzae.* Nonhemolytic streptococci, *Streptococcus viridans,* and hemolytic streptococcus were found in about one half the cases. Approximately one fourth of the entire group showed pneumococci.

Etiology. Table 6 shows the distribution of cases according to predisposing disease and complication of allergy and sinusitis. Fifty-five of the total 75 patients had an associated major respiratory allergy including bronchial asthma, perennial allergic bronchitis, and severe perennial allergic

TABLE VI

Summary of Treatment

Twenty-Three Cases Treated with Sulfonamides per se; 21 Patients Treated by Allergy Management per se; and 31 Patients Treated on a Combined Management of Allergy and the Use of Sulfonamide Drugs

Treatment	Period of Observation	Total Treated	Improvement				No Improvement	Died
			Total	Complete	Marked	Moderate		
Sulfonamide drugs	4 Months to 4 Years	23	22	7	12	3	1	
			17 Required more than 1 course of sulfonamide. 6 Showed improvement after 1 course of sulfonamides for periods from 1–2½ years (except 1 observed for 4 months). 11 Had no exacerbations and continued to improve during entire period of observation. 1 Had other therapeutic measures, i.e. postural drainage.				Symptoms not controlled with 3 courses of treatment	
Allergy management	1 Year to 4½ Years	21	15	4	5	6	5	1 Cause unknown
			8 Showed continued improvement of cough for 1–4 years. 7 Had recurrence of symptoms. 3 Recurrences associated with discontinuance of hyposensitization program.					
Sulfonamide drugs combined with allergy management	6 Months to 5 Years	31	26	5	14	7	5	
			10 Showed no exacerbation. 16 Reported recurrences of symptoms. Recurrences occurred with discontinuation of allergy program and too wide intervals between sulfonamide courses. 10 Had continued improvement for as long as 4½ years.					

rhinitis. However, of a total of 190 consecutive cases of bronchiectasis seen at the Clinic over a five year period 92 had major respiratory allergy of sufficient severity to require medical consultation.

The cases following whooping cough or measles were probably complicated by an undiagnosed bronchopneumonia.

An interesting relationship between sinusitis and allergy was noted in this study. Of 30 cases having definite recurrent or chronic sinusitis, all but two had an accompanying major respiratory allergy consisting of allergic bronchitis or bronchial asthma or both, almost always accompanied by

perennial allergic rhinitis. Six had severe perennial allergic rhinitis without other respiratory allergy.

Treatment

Palliative treatment was used to reduce pulmonary infection to a minimum and to eradicate any cause of bronchial obstruction in order to produce an asymptomatic phase without cough, expectoration, hemoptysis, or toxicity. Sulfonamide drugs and allergy management were the chief therapeutic measures used.

In general the treatment used was as follows:

1. Sulfonamide drugs only were used in 23 cases, of whom 19 were nonallergic individuals and four had moderately severe allergies consisting of perennial allergic rhinitis in three and perennial allergic bronchitis in one. Sulfathiazole or sulfadiazine was used in most instances; in a few cases sulfanilamide or sulfapyridine was used. The average "course" consisted of 7.7 grains of the drug four times daily for four weeks. The courses were repeated from 0 to 9 times, usually at intervals not less than every three or four months. In one case direct intrabronchial instillation of sulfathiazole was done with remarkably good results.

2. Allergy management only was used in 21 cases in which a respiratory allergy was suspected of being an etiologic or complicating factor in the production of symptoms. After thorough allergy investigation the therapeutic program consisted of avoidance of the important offending allergens in the patient's environment, dietary restrictions, hyposensitization with extracts containing the major exciting allergens, and autogenous vaccine incorporated in the hyposensitization program where significant sensitivity was manifested by intradermal reactions. These measures were followed for periods varying from four months to three and one-half years.

3. In the third group of 31 patients a combined treatment of sulfonamide drugs and allergy management constituted the chief therapeutic measures.

Postural drainage was used in 59 patients; 11, however, discontinued it after a short time because they did not find it beneficial. The patients were instructed to invert the chest completely for 10 or 20 minutes two or three times daily. Some were advised to have the foot of their bed raised during the night. Expectorants were prescribed for use prior to postural drainage exercises to aid in the drainage of tenacious sputum. For purposes of comparison postural drainage was not advised in 16 cases regardless of the amount of expectoration.

Treatment of sinusitis and oral sepsis were instituted to eradicate possible foci of infection whenever it was indicated.

General supportive measures such as rest, adequate diet, and vitamins were used as indicated to improve general health.

In one case roentgen-ray treatment had been used without benefit.

In several of the 12 patients having fusiform bacilli and spirochetes in their sputum, neoarsphenamine had been used without apparent benefit.

Results

The results in this study were evaluated entirely by symptomatic relief as manifested by improvement of cough and the amount and character of the expectoration. Improvement of toxic symptoms and general health was usually in proportion to improvement of cough and expectoration. Evaluation was not based upon a comparison of symptoms before and after acute exacerbations, but upon an estimation of the effect of allergy management and sulfonamide therapy in the alleviation of chronic symptoms of bronchiectasis and prevention or reduction of exacerbations.

Results were classified as follows:

1. Complete improvement or 100 per cent relief of cough and expectoration.
2. Marked improvement with cough and expectoration reduced at least 75 per cent and the character of the sputum almost always nonpurulent.
3. Moderate improvement with 50 to 75 per cent reduction in cough and expectoration.
4. Slight improvement with 25 to 50 per cent reduction in cough and expectoration.
5. No appreciable improvement in symptoms or bronchiectasis or symptoms even becoming worse.

Comment

The most dramatic results were obtained in the group receiving sulfonamide drugs both in the allergic and in the nonallergic group. The recent work of Norris [9] indicates that when sulfadiazine is given orally significant concentrations can be found in the sputum regardless of the amount of expectoration. Repeated courses of sulfonamide drug in dosage sufficient to maintain adequate blood levels, continued long enough to secure maximal improvement, and given not more often than every three to four months is probably the method of choice rather than continuous small doses, because there is less danger of producing untoward reactions and of causing the bacteria to become sulfonamide resistant. In this series, as far as is known, only three had toxic manifestations from the sulfonamide drugs. Because of its low toxicity sulfadiazine is, of course, the drug of choice. Sulfonamide blood levels were not obtainable, since in all but a few cases the drug was administered by the local doctors.

The period of observation particularly for those in whom sulfonamide drugs were used without allergy management was a relatively short period during which time it was necessary to repeat the course in some cases a number of times; this raises the question whether or not sulfonamide drugs could be given at sufficiently short intervals to maintain improvement of symptoms of bronchiectasis over a period of many years.

An attempt to evaluate the results of treatment in the group of patients receiving both chemotherapy and allergy management was difficult. On the

whole the best results seemed to occur when the two were used simultaneously. It was found that in some cases greater improvement occurred after allergy management had been instituted than had been experienced with the use of sulfonamide drugs alone. On the other hand allergy management frequently gave poor or only fair results until sulfonamide drugs were also used. Whether or not sulfonamide drugs needed to be used in addition to allergy management seemed to depend upon the general health of the patient and upon the severity of his symptoms; however, this was not always true.

Another logical form of treatment to prevent stagnation of bacteria laden secretions is postural drainage exercises. In the majority of cases it was believed to be of definite help in producing temporary symptomatic relief. In the 16 patients who did not do postural drainage exercises at all, there seemed to be no apparent difference in the good results regardless of the amount of expectoration. The same appeared to be true of those who discontinued it of their own accord after only short periods of trial because they did not find it helpful. Others served as their own control in this variable, since they had carried out vigorous postural drainage exercises for a sufficiently long time to obtain maximum relief from this procedure before allergy or sulfonamide treatment was instituted.

No control series is included in this study; it is well known that the disease is chronic and characterized by frequent exacerbations. It was believed that no series of cases would be strictly comparable with one which included so many variables. Since at least 75 per cent had symptoms of bronchiectasis from five to forty-five years they were their own best controls. In making comparisons before and after treatment an attempt was made to determine the average amount of cough and expectoration that had been experienced between exacerbations to see if by controlling complications and by treating the pulmonary infection directly with chemotherapy, there would be improvement of the chronic symptoms as well as reduction in the number of exacerbations.

It may be concluded that the results of this study indicate that all cases having symptoms of bronchiectasis which are nonsurgical should, unless otherwise indicated, be given adequate trial on sulfonamide therapy and that those in which a complicating or etiologic factor is an allergy of the respiratory tract should be placed on allergy management. In the majority of cases improvement entailing at least 50 per cent reduction in cough and expectoration occurred. Exacerbations were frequent in all groups but almost invariably if sulfonamide drugs were repeated when symptoms first began to return to their former severity, continued improvement could be maintained. Likewise, exacerbations occurred often when the allergy program was discontinued.

Summary

1. Of 190 consecutive cases of bronchiectasis it was found that approximately one-half had major allergy of the respiratory tract. A clinical study

was made of 75 selected cases of bronchiectasis to evaluate sulfonamide therapy and allergy management in treatment. In 55 of these cases an allergy of the respiratory tract was an etiologic or complicating factor.

2. Twenty-three cases received sulfonamide drugs as the chief or only therapeutic measure and were observed for four months to four years. Twenty-two of these patients showed definite improvement with reduction of cough and expectoration.

3. Twenty-one cases treated chiefly or wholly with allergy management were observed for a period of time ranging from one to four and one-half years. Fifteen of this group showed frank improvement with reduction in cough and expectoration.

4. In 31 cases combined allergy and sulfonamide therapy was used. Twenty-six cases were found to have at least 25 to 100 per cent improvement in cough and expectoration. They were observed for six months to five years.

5. Recurrences of symptoms of original severity were frequently noted following acute respiratory infection, cessation of allergy management, or in some cases when infrequent courses of sulfonamide drugs were used.

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CASE REPORTS

STREPTOBACILLUS MONILIFORMIS AS A CAUSE OF SUBACUTE BACTERIAL ENDOCARDITIS: REPORT OF A CASE TREATED WITH PENICILLIN *

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HUMAN infections with the *Streptobacillus moniliformis* have occurred either following a rat bite,[1] or as epidemics of so-called Haverhill fever, presumably due to infected milk.[2] Regardless of source, the clinical picture resulting from infections with this organism is one of an acute infection with abrupt onset, and characterized by chills, relapsing fever, generalized rash and involvement of joints.[3] In the epidemic form, which is generally milder, there have been no deaths, and hence no autopsy material for study has been available.[4] Deaths have occurred from the infection acquired through rat-bite, and a few postmortem examinations are available.[1, 4, 5, 6] The findings, in general, have been similar to those present in other acute bacterial infections, but in two instances acute ulcerative endocarditis has been described.[1, 5] In contrast to those types of infection, Stuart-Harris and associates in 1935 [7] reported a case of streptobacillus infection in an 18 year old boy with previous rheumatic heart disease, in which the presenting picture was that of subacute bacterial endocarditis. We have recently encountered a similar case which constitutes the basis for this report.

Reports of Cardiac Involvement Following Rat-Bite. In 1916, Blake [1] made the first report of the postmortem findings of a case of *Streptobacillus moniliformis* infection following rat-bite. The patient was a 67 year old woman who died after a two week febrile illness. She had had no symptoms of heart disease, and no cardiac abnormalities were present on physical examination other than a soft systolic apical murmur. There were no embolic phenomena, but shortly before death the murmur became louder and harsher. The *Streptobacillus moniliformis* (known at the time as the *Streptothrix muris ratti*) was isolated from the blood during life. At postmortem examination, the heart weighed 360 gm. and the musculature was normal on gross examination. On the posterior cusp of the mitral valve, there was a large (15 by 7 mm.) vegetation which had ulcerated through the valve leaflet. On microscopic examination, "masses of organisms appearing as long slender bacilli" were demonstrable in necrotic areas of the vegetation. The aortic, pulmonic and tricuspid valves were normal. Infarcts of spleen and kidney were present. In addition to the endocarditis, a subacute myocarditis with microscopic areas of focal necrosis was present. Re-

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The sodium salt of penicillin used in the treatment of this patient was obtained from Dr. Chester S. Keefer, Chairman of the Committee on Chemotherapeutics and Other Agents, of the National Research Council.

cently, with Horstmann and Arnold, Blake [4] has reported another fatal case of *Streptobacillus moniliformis* infection following rat-bite, in which the important histological finding was this focal myocarditis. No endocarditis was present.

In 1941, Rountree and Rohan [5] reported a fatal infection with *Streptobacillus moniliformis* in a 14 year old girl following contact with a rat. Although a cardiac murmur had been noted at the age of six, there had been no symptoms of heart disease, nor was any evidence of antecedent cardiac disease noted at autopsy. In addition to the relapsing fever, rash, and joint pains characteristic of this infection, endocarditis was evident from the presence of a loud apical

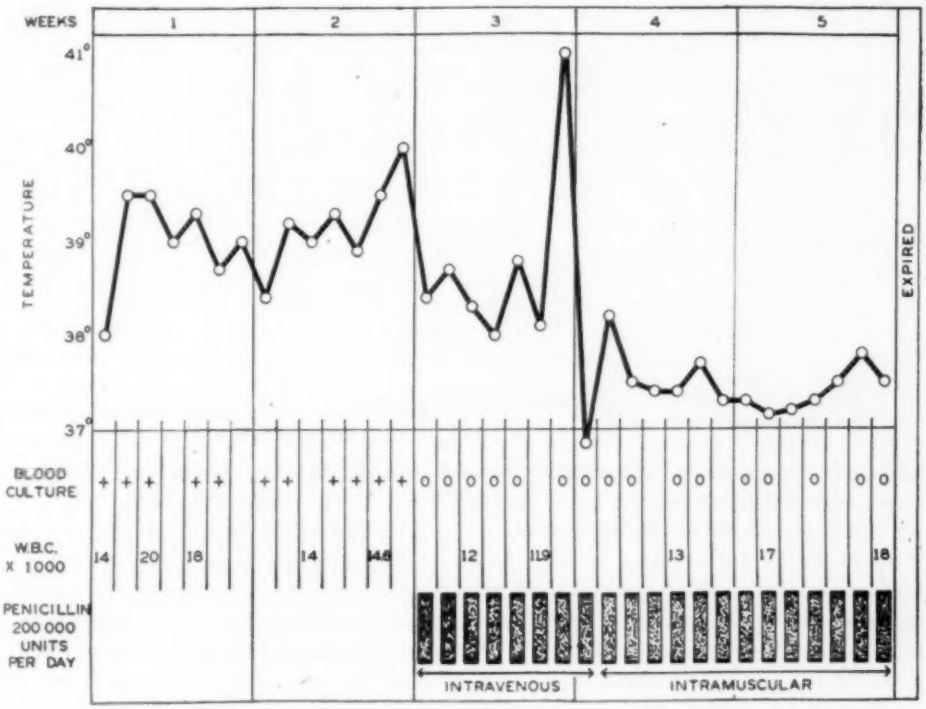

FIG. 1. Clinical course of patient with subacute bacterial endocarditis caused by *Streptobacillus moniliformis*.

systolic murmur, subungual hemorrhages, and signs of an arterial embolus in the right leg. At postmortem examination, the only cardiac abnormality was a large (3.0 cm.) vegetation on the mitral valve which "had ulcerated through the cusp onto the upper part of the ventricular wall." The spleen was greatly enlarged and contained numerous infarcts. Although two antemortem blood cultures were sterile, the *Streptobacillus moniliformis* was isolated in pure culture from the vegetation on the heart valve.

In a footnote in their comprehensive review of rat-bite fever, Brown and Nunemaker [3] state that unpublished autopsy reports of two fatal cases of *Streptobacillus moniliformis* infection have been brought to their attention. In one, a myocardial abscess was present. Since the other is described as "a patient who

TABLE I

Media	Penicillin Concentration in Oxford Units						
	1.0	0.1	.05	.01	.001	Control	Hours
4% serum broth	0	0	—	0	—	3+	24
	0	0	—	2+	—	4+	48
	0	0	—	4+	—	4+	72
Thioglycolate 5% serum	—	0	0	±	2+	2+	24
	—	0	0	±	2+	2+	48
	—	0	0	1+	4+	3+	96
Blood agar plates incubated under 10% CO_2 for 38 hours							24
	0	0				3+	48
	0	0		±	2+	3+	72
% blood broth incubated under 10% CO_2 for 38 hours							24
	0	0		±	1+	2+	48
	0	0		±*	1+†	2+	72

Growth recorded 1 + to 4 +.
* Subculture on serum enriched thioglycolate negative.
† Subculture positive.

had had endocarditis," it probably resembles the clinical type of subacute bacterial endocarditis reported by Stuart-Harris and the present authors.

Subacute Bacterial Endocarditis. The only published report of this type of streptobacillus infection is in the paper of Stuart-Harris and his associates.[7] Unfortunately, as the emphasis in their report was on the bacteriology of various unusual organisms isolated from patients with endocarditis, the clinical and pathological findings of the patient with streptobacillus infection are merely summarized in one paragraph:

"Walter Gooding, aged 18, was admitted to Hackney Hospital on 27th October 1934, suffering from subacute bacterial endocarditis. He died on 25th November 1934 and the post-mortem findings were typical of this condition supervening on chronic rheumatic endocarditis. An organism, which is of interest in view of its extreme pleomorphism, was isolated aerobically on three occasions during life by blood culture, and appeared in direct films and cultures from the aortic and mitral valves at autopsy. The patient's blood count showed a considerable degree of anemia of the secondary type, accompanied by a moderate polymorphonuclear leucocytosis."

From the detailed description of the bacteriology of this organism, there can be little doubt that it was the *Streptobacillus moniliformis.*

CASE REPORT

P. W., a 43 year old supervisor of male nurses, was admitted to the medical service of the New York Hospital on March 4, 1944.

Chief Complaint: Fever and weakness of two months' duration.

Past History: The patient had had no significant illnesses other than two attacks of rheumatic fever at the ages of 16 and 30. Both attacks were similar and consisted of the development of swollen, painful, red, hot and tender knee and finger joints associated with fever. Following the first attack, which had occurred in Ireland, he was told that he had a heart murmur, but at no time prior to his present illness had he had any symptoms suggestive of heart disease or had he modified his activity in any way.

Present Illness: In October 1943 (four months prior to admission to New York Hospital) the patient's wife first noticed that he seemed fatigued and had developed a hacking non-productive cough associated with night sweats. In December 1943, the patient first noticed that he was very tired each day after work, was having frequent copious night sweats, and would have minimal swelling of the ankles only in the evening and unassociated with any cardiac symptoms. He stopped work in January 1944 because of easy fatigability, fever, headache, and stiffness of knee and ankle joints. During January and February the intermittent fever continued (maximum of 40.4° C.) and he experienced migratory pains in the knees, toes and fingers with no objective evidence of involvement of the joints. The onset of these pains would be sudden and acute, gradually diminishing over a 24 to 48 hour period. With these episodes of pain, his temperature would increase to a higher level, and on one occasion the tip of the first left finger was swollen and tender for 48 hours.

During the two week period before admission, he had had an episode of sudden severe pain in the left upper quadrant which had gradually disappeared over five days, and a 24 hour period during which he had had difficulty in "pronouncing words."

Although with the fever he had noticed cardiac palpitation, he had had no dyspnea, orthopnea or substernal pain. During a four day period which ended one week before admission, the patient received 10.0 gm. of sulfathiazole and 17.0 gm. of sulfadiazine without any noticeable effect upon his symptoms. The only skin abnormality noted during the entire illness was a transient macular rash over the right buttock and calf which was associated with, and apparently due to the administration of, sulfathiazole.

Contact with Rats: The patient was employed in a State Hospital, housed in old buildings which contained rats. Two years before his present illness, armed with a broomstick, he had killed a large brown rat in one of the buildings. He stated that he had not handled the animal or the contaminated end of the broomstick, and that since that time to his knowledge he had had no contact with rats whatsoever.

Physical Examination: The patient was a thin, sallow, well-developed, middle-aged white male who appeared to be chronically ill but in no distress. The respirations were rapid but he did not appear to be dyspneic. There was no orthopnea or cough. Temperature was 38° C.; pulse rate, 112; respiratory rate, 28. Blood pressure was 140 mm. Hg systolic and 40 mm. diastolic.

There were no petechiae on the mucous membranes or on the skin, which was pale and sallow. On the lateral aspect of the right calf and over the right buttock there were a few 1 to 2 mm. discrete faded pink papules, some of which were excoriated.

The eyes, ears, nose, mouth and throat were negative. The veins in the neck were not distended. Accentuated systolic arterial pulsations were present. There was no enlargement of the superficial lymph nodes.

The chest was resonant, and the breath sounds were vesicular. A few distant fine râles were heard at the left base.

The cardiac impulse was visible over the fourth and fifth interspaces on the left. The heart was enlarged, the left border of dullness extended to the anterior axillary line in the fifth interspace. The sounds were regular in force and rhythm. At the apex, presystolic and systolic thrills were palpable and a rumbling presystolic murmur which ended in a high pitched blowing systolic murmur was heard. Over the aortic

area and down the left sternal border, somewhat lower pitched blowing systolic and diastolic murmurs were present. There were no thrills over the aortic area. The peripheral signs associated with aortic insufficiency were present.

The abdomen was flat; neither the liver nor the spleen was felt. There was marked clubbing of the fingers.

The only abnormalities noted on neurological examination were a slight weakness of the left corner of the mouth, and an extensor plantar response of the left great toe when the sole of the foot was stroked.

Laboratory Examinations. Blood: Hemoglobin was 9.5 gm.; red blood corpuscles 2,900,000 per cu. mm.; white blood corpuscles 14,000 per cu. mm.; neutrophiles 75 per cent (nonsegmented forms 20 per cent); lymphocytes 20 per cent; large mononuclears 2 per cent; eosinophiles 1 per cent.

Urine: Yellow, clear, acid, specific gravity 1.012, albumin 0, sugar 0; sediment: occasional white blood corpuscle.

Blood Cultures: Streptobacillus moniliformis was recovered in pure culture on 11 separate occasions between March 4 and March 16 inclusive. Sixteen blood cultures taken from March 17 to April 7 inclusive were sterile (during penicillin therapy).

Roentgen-ray: Examination of the chest on March 4, 1944, showed marked cardiac enlargement with an enlarged left auricle and prominent pulmonary markings due to congestion.

Electrocardiogram: On admission, before digitalization, there was beginning deviation of the electrical axis to the right and minimal splitting of the QRS complexes. Electrocardiograms taken after digitalization and as the disease progressed showed evidences of overdigitalization and progressive myocardial damage.

Course of Illness: During the first two weeks in the hospital, the patient's fever continued with daily elevations to 39.4° C., and embolization of the tips of several fingers and toes occurred. When it was established that penicillin inhibited the streptobacillus in vitro, therapy with this agent was started on the fourteenth hospital day. He received 200,000 Oxford units daily for a period of 21 days. The material was administered by continuous intravenous drip for the first eight days, and by the intramuscular route for the succeeding two weeks. No heparin was used.

During the first week of therapy, the patient's fever started downward, and during the second and third weeks his temperature was only rarely above normal. With the exception of one conjunctival petechia which appeared the day after penicillin was started, no definite evidence of further embolization appeared. All 16 blood cultures taken after the institution of therapy were sterile. However, despite the marked improvement in the signs of the infection, the patient gradually developed cardiac failure which was steadily progressive and resulted in death on April 9.

Clinical Diagnosis: Rheumatic heart disease with stenosis and insufficiency of mitral and aortic valves; subacute bacterial endocarditis (*Streptobacillus moniliformis*).

Autopsy Protocol: Autopsy was performed six hours post mortem. There were no abnormalities of the skin, eyes, ears, nose, throat or superficial lymph nodes. There were no adhesions or free fluid in the abdominal cavity. There were 1,100 c.c. of fluid in the right pleural cavity and 900 c.c. in the left pleural cavity. There were 75 c.c. of fluid in the pericardial cavity. The parietal pericardium was gray-white, smooth and glistening.

The heart weighed 600 grams. The epicardium was glistening, transparent, and contained a moderate amount of fat in the coronary sulci. The right ventricular wall measured 5 mm. in thickness. The left ventricular wall measured 14 mm. in thickness. The myocardium was red and soft. No infarcted areas were seen. The myocardium of the left ventricle was split, and appeared red with some small yellow

areas. The tricuspid valve measured 14 cm. in circumference, pulmonic 9 cm., mitral 12.5 cm., and aortic 8.5 cm. The tricuspid and pulmonic valve leaflets appeared thickened and stretched. On the mitral valve cusp edges there were collections of irregular, crumbly, friable material which was fairly adherent. The chordae tendineae were not thickened or shortened. In fact, many of them were stretched, and some had ruptured. Some of them were also encrusted with vegetations. The endocardium of the left auricle above the posterior leaf of the mitral valve appeared slightly thickened, but no vegetations were present. The aortic valve at first glance had the appearance of a bicuspid valve. This was because two of the commissures of the cusps had been destroyed, so that there was practically a total obliteration of the space between two of the cusps. The valve leaflets were also thickened and encrusted with more of the vegetations. The left circumflex coronary artery had its origin adjacent to that of the right coronary artery.

Microscopic Examination: Section of the myocardium in the left ventricle showed the myofibrils to be hypertrophied and fragmented in many areas. Fibrous tissue deposition was widespread. There were many focal accumulations of lymphocytes around vessels, especially in the fibrotic areas.

A section of myocardium stained with Sudan III showed a marked deposition of fat in the myofibrils underneath the ventricular endocardium.

Examination of the other organs disclosed infarcts of the spleen and left kidney, slight arteriosclerosis of the aorta, and the characteristic changes of chronic passive congestion in the lungs.

Bacteriology: The initial blood culture (March 4) in standard beef-heart-infusion broth showed no growth. In a second culture (March 5) in this same medium, tiny white granular "balls" appeared, resting on the undisturbed sedimented blood cells after five days of incubation. Gram stains of these colonies, picked up with a long slender capillary pipette, showed short chains looped about the blood cells. These were at first mistaken for cocci, but, on further observations, gram-variable streptobacilli, diphtheroid and other pleomorphic forms were seen. All 11 blood cultures on this medium taken prior to penicillin therapy presented the same findings.

Subcultures of this "ball" growth were made in duplicate on various media, one set enriched with blood or serum, the other without enrichment. The serophilic nature of the organism was evident when good growth and marked pleomorphism occurred in the enriched media whereas all subcultures on unenriched media were uniformly sterile. Incubation with 10 per cent CO_2 improved growth somewhat, but was not essential. Transplants were made daily to ensure viable cultures. Loeffler's serum and dextrose-starch-serum-agar were selected for subsequent cultures. The former proved highly satisfactory for the development of the large disc-like forms referred to by Klieneberger as "L" forms. The dextrose-starch-serum agar supported growth, not only of the larger, but also of the pinpoint colonies designated as "L–1." All of the classical forms of the *Streptobacillus moniliformis* described originally by Schottmüller [8] and Blake [1] and the forms subsequently described by Klieneberger [9] developed on these two media. The characteristic marked pleomorphism was shown by the presence of long and short filaments, with terminal and sub-terminal swellings, sometimes projecting from one side only; fragmented forms with the appearance of streptococci, a variety of diphtheroid, club-shaped and coccobacillary forms, and an occasional "snake-like" form.

Postmortem Cultures: Blood cultures taken from the heart showed no growth. Cultures from vegetations of mitral and aortic valves were unfortunately so heavily overgrown with *E. coli* and other postmortem invaders that repeated attempts to isolate *Streptobacillus moniliformis* proved unsuccessful.

Numerous typical forms, however, were seen in stained contact films, as also in stained preparations from suspensions of ground-up tissue from these valves, sug-

gesting that these organisms were still present, and presumably viable, in the heart valves at the time of the patient's death.

Penicillin Sensitivity: In vitro tests of the sensitivity of the organism to penicillin were made in enriched media under conditions most favorable for growth. Serial dilutions of penicillin were incorporated in the various media before inoculation with the streptobacillus, and, in every test, a good growth was obtained in the control tube. The tests were read at (approximately) 24, 48, and 72 hours. Although in certain media the organism will die off if not transplanted after 24 hours, in broth and thioglycolate enriched with serum, growth appeared between 24 and 48 hours in the higher dilutions of penicillin.

At 72 hours, the organism was completely inhibited by 0.1 unit of penicillin in all of the media used. This degree of penicillin sensitivity in vitro is of the same order of magnitude as is usually found by this technic for most of the non-hemolytic streptococci isolated from patients with subacute bacterial endocarditis.

Virulence for Mice: Six mice * were inoculated intraperitoneally with amounts of culture (seventieth generation) varying from 0.5 to 1.0 c.c. In three animals the inoculum was from a 4 per cent serum enriched broth culture; in the other three, washings from a blood agar slant were used. The animals were observed for 44 days, during which time there was no evidence of arthritis. Blood cultures (serum broth) on the third, fifth, seventh and seventeenth days, as well as cultures of heart's blood on the forty-fourth day, were all sterile. Another mouse, which had been inoculated intraperitoneally with 0.5 c.c. of an actively growing culture (approximately the twenty-fifth generation), developed no signs of arthritis and was alive three months after inoculation.

Brown and Nunemaker [3] emphasize the fact that after repeated passage (400 generations) on artificial media, the *Streptobacillus moniliformis* will lose its virulence for mice and will not regain it even after repeated animal passage. However, they routinely used about the fiftieth generation for the production in mice of chronic infection with arthritis and bacteremia. Therefore, it would seem that the strain isolated from this patient with a chronic infection was either truly avirulent for mice or lost its virulence on artificial media more rapidly than is usual.

Discussion

The postmortem findings in this patient were quite similar to those found when subacute bacterial endocarditis is caused by the implantation of a non-hemolytic streptococcus on a valve previously damaged by rheumatic fever. The clinical course also was identical with that customarily seen in subacute bacterial endocarditis, and quite unlike the usual *Streptobacillus moniliformis* infection, whether acquired through rat-bite, or in the form of Haverhill fever. It differed from the usual infection in the insidious onset, the absence of arthritis and the absence of a rash. (The joint symptoms experienced by the patient were apparently embolic in origin.) However, this case is quite similar in essential details to the case reported by Stuart-Harris and his associates.

Since one form of this markedly pleomorphic organism deceptively resembles a gram positive coccus both in culture and in tissue sections, it is possible that subacute endocarditis caused by it could be mistakenly regarded as streptococcal. For this reason, one might expect that the incidence of streptobacillus involve-

* CFW, a virus-susceptible strain of mice, obtained from Carworth Farms, New City, New York.

ment of previously damaged heart valves is actually more frequent than is reflected by the single previous report.[7]

For a detailed description of the biology of this organism, the recent authoritative monograph of Brown and Nunemaker[3] should be consulted. The *Streptobacillus moniliformis* is one of the most pleomorphic organisms known, and depending somewhat upon environmental factors, may appear as round bodies which simulate a coccus, or as long filaments. These may fragment, thus simulating chains of bacilli or cocci, or may show various fusiform or round swellings. In the strain isolated from our patient, the round coccal forms were gram positive, whereas the filamentous forms were gram negative. In addition to these forms, the streptobacillus can develop into a so-called L-1 or pleuropneumonia-like form. The exact morphology of this form is obscure because of its size, which is sufficiently small to allow passage through filters capable of holding back most bacteria. On solid media it forms colonies which are microscopic in size in early growth but later become visible macroscopically. Some controversy exists as to whether this L-1 form is a part of the life cycle of the streptobacillus or is a symbiont of it.[9] Brown and Nunemaker have reviewed the evidence pro and con, and, in the light of this and their own experiments, conclude that this pleuropneumonia-like microörganism is in fact one stage of the life cycle of the streptobacillus. They also believe that this L-1 form is the essential structure upon which the streptobacillus depends for survival, and that the organism usually exists in this L-1 form in infected human and animal tissues.

The streptobacillus will not grow in meat infusion broth unless it is enriched with serum or ascitic fluid. For this reason, as emphasized by Brown and Nunemaker, in patients with streptobacillus infections of the rat-bite or Haverhill type, blood cultures taken by the usual routine technics are seldom positive. The relative ease with which positive blood cultures were obtained from this patient is probably due to the fact that bacterial endocarditis was present, a lesion which usually makes positive cultures more readily obtainable than from bacteremias of other sources. The enrichment supplied to the primary cultures by the patient's own serum may have played some part, however, since all transplants from the original cultures to identical media which did not include this factor, were uniformly sterile.

Various chemotherapeutic agents have been used in the treatment of streptobacillus infections of man with indifferent success.[3] There is no evidence that the sulfonamide derivatives exert any therapeutic effect on human or animal infections with this organism.[3, 10] In a few instances of human infection, neoarsphenamine has been tried,[3, 11, 12] but no definite evidence of therapeutic effect was demonstrable, and it exerts no protection against the experimental infection in mice.[10] Brown and Nunemaker and Heilman found that various gold preparations (sodium aurothiomalate) had a striking effect on experimental infections in mice of the acute type. However, in the chronic type of experimental infection produced by less virulent (fiftieth generation) cultures of the streptobacillus, gold therapy was without effect.[3]

It is, therefore, of considerable interest that the streptobacillus isolated from this patient with endocarditis was apparently inhibited by penicillin both in vitro and in the patient. Unfortunately, because of the lack of virulence for mice (by the twenty-fifth generation), it was impossible to investigate the effects of

penicillin on this strain in the experimental animal. Because of the existence of the L-l form, more extensive investigations will have to be made before it can be concluded with certainty that the *Streptobacillus moniliformis* is completely inhibited by penicillin. However, further evidence to this effect has been supplied recently by Heilman and Herrell,[18] who found that mice infected with a young culture of streptobacillus all survived the acute infection when treated with penicillin. In a few of the survivors, arthritis developed, and in only one of 12 spleens examined from the treated group, were the organisms obtained by culture.

However, the possibility exists that penicillin may inhibit only the streptobacillus or "flowering" form of the organism's life cycle, while allowing the hardier L-l form to survive. This question is under investigation at present.

It is impossible to decide whether this patient's endocarditis was significantly affected by the penicillin therapy. The clinical signs of infection disappeared promptly after treatment was begun, but valvular vegetations, in which the organisms could be demonstrated by staining, were still present after three weeks of therapy. It is conceivable that further penicillin therapy might have eradicated the infection of the valve, had not cardiac failure supervened. The development of cardiac failure, which is apparently due for the most part to the additional valvular damage caused by the bacterial infection, is not infrequently encountered in the sulfonamide or penicillin therapy of bacterial endocarditis, and is one of the important limiting factors in such therapy.

Summary

A case of *Streptobacillus moniliformis* infection is reported, in which the clinical and postmortem findings were those of a subacute bacterial endocarditis, which had involved heart valves previously damaged by rheumatic fever. The literature concerning acute and subacute endocarditis caused by this organism is reviewed. Evidence that the organism was inhibited by penicillin is presented.

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PRIMARY BRONCHOPULMONARY ASPERGILLOSIS, AN OCCUPATIONAL DISEASE *

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ALTHOUGH pulmonary aspergillosis can no longer be considered a rare condition, in view of the increasing number of cases being reported in the literature, its consideration as a disease peculiar to certain occupations has been generally overlooked. Historically, the first recorded case is attributed to Hughes Bennett in 1842. In 1890 Dieulafoy, Chantmesse and Widal described several clinical cases in persons engaged as pigeon fatteners in Paris.[1] In 1897 Renon considered it as a trade disease in persons working as pigeon feeders. In this occupation the individuals engaged as pigeon stuffers crammed the beaks of the birds with a mixture of grain and water from their own mouths and some developed a severe form of mycotic pseudotuberculosis. He also considered pulmonary aspergillosis as a trade disease among the wigmakers who engaged in the task of combing the hair with rye meal to remove the fat.[2]

I wish to add another case to the growing literature. This case is unique in that, as far as I am able to determine, it is the first in the history of this country to be heard before the Industrial Commission of a sovereign state and to be declared as an occupational disease and, therefore, compensable under the laws of the state.[3]

CASE REPORT

The patient D. F., male, aged 47 years, was seen by me on January 7, 1942, and presented the following complaints: productive cough, shortness of breath and marked weakness of 10 years' duration, and inability to work because of these symptoms. About 10 years previously he began to cough and whereas at first it occurred only in occasional paroxysms, it became progressively more severe so that now it was constantly present. The cough had always been productive, occasionally of a black, streaked expectoration, and had never been associated with hemoptysis. Coincidentally, he began to note some shortness of breath on effort; this, too, became progressively worse and was now constant, even at rest. These symptoms, together with weakness, loss of weight and anorexia, became so severe that it was difficult for him to engage in any work involving even the slightest effort.

* Received for publication September 25, 1944.

He was employed at the Union Stock Yards in varying capacities for approximately 20 years. His work at all times brought him into intimate and prolonged contact with animals and with heavy concentrations of dust, the dust of the Yards being mixed with that of hay, grain, corn and straw used for the animals. Part of the time he worked in the animal chutes, in the hog house, as yard master, as animal unloader and cattle yardener, etc.

Physical examination revealed a white male who was obviously dyspneic, even at rest. The face presented a florid cyanosis and audible rhonchi were evident at least five feet from the patient. The superficial veins of the anterior thorax were prominent and a bilateral respiratory lag was noted. Breathing was mainly of the abdominal type. Tactile fremitus was decreased, hyperresonance was obtained on percussion, and sibilant and sonorous râles were audible throughout both lungs. The heart was not enlarged, blood pressure was 115 mm. Hg systolic and 80 mm. diastolic and pulse 110 per minute.

Roentgen examination of the lungs showed emphysema with increased pulmonary linear striations, especially or the left side; adhesions of the left diaphragm near the cardiac apex; pleural thickening in the upper chest on both sides, especially the left; and massive lung root shadows, especially on the right.

Sputum examination and cultures were made and a typical *Aspergillus fumigatus* was isolated. The tuberculin patch test was definitely positive and a scratch test for *Aspergillus fumigatus* was questionably positive.

Comment

The history, physical examination and roentgen-ray study were indicative of a far advanced pulmonary fibrotic condition with pleural and bronchial involvement. The clinical picture resembled that of tuberculosis, but careful study here and elsewhere eliminated this diagnostic possibility because of the repeatedly negative sputa for tubercle bacilli and a conspicuous paucity of calcified shadows in the roentgenogram such as are often seen in chronic pulmonary tuberculosis. Careful questioning elicited the further facts that in June, 1941 he was studied at the Hines Veterans Hospital where a diagnosis of pulmonary aspergillosis was made and treatment instituted.

Proceedings were instituted before the Industrial Commission of the State of Illinois on the basis that the pulmonary affliction arose specifically out of the nature of the work being done for many years, i.e., the disease was peculiar to the occupation. The case was heard on arbitration on June 8, 1942, and the arbitrator's decision was filed with the Industrial Commission, giving an award to the petitioner. On review, the Industrial Commission upheld the award.[3]

Discussion

Michaeli, in 1725, first described the genus Aspergillus, of the family Aspergillacae, order Aspergillules, class Ascomycetes.[4] It is a regular inhabitant of soil and is frequently isolated from cereal products, unmilled grain, hay and other stock feeds, the spores being mingled with grains, seeds and flour. Of the many species of this mold, only a few are pathogenic. *Aspergillus fumigatus* is the most common offender in infections of the bronchopulmonary tissue.[5] However, occasional cases due to *Aspergillus niger* are reported.[6, 7] Pigeons, canaries, penguins, ducks and chickens are most often affected. Man is relatively immune and classic instances are found in certain occupations which involve pro-

longed and intimate contact with grains or birds. Thus farmers, feed mill workers, and threshers are prone to infection. Certain dusts are also important, such as that developed in wig preparation and that produced by sponge cleaners who beat dried sponges.[1]

The principal factor in the pathogenesis of the disease in man seems to be exposure to repeated massive dosages. In such instances, the condition may be primary without any preceding pulmonary disease. Under other conditions, however, the factor of constitutional or local predisposition may be the determining one. Not infrequently, therefore, aspergillosis may be engrafted on previously diseased bronchopulmonary tissue as a secondary infection. Uncontrolled diabetes, dysentery, enteritis, cirrhosis and tuberculosis have been cited as predisposing causes,[8] as well as carcinoma [9, 10] and bronchiectasis.[7] As a result of such association of diseases, the theory has been advanced that pulmonary aspergillosis does not develop in man unless local or constitutional resistance is lowered by some preëxisting condition. That this is not necessarily true is attested to by the case herein reported and by the number of cases in the literature without evidence of any other pulmonary disease process.

Conclusion

A case of primary pulmonary aspergillosis is herein reported in a man who worked at the Union Stock Yards for approximately 20 years. As far as can be determined, this is the first such case to be tried before the Industrial Commission of a sovereign state and to be declared an occupational disease.

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INTERLOBAR EFFUSION ASSOCIATED WITH CONGESTIVE HEART FAILURE *

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Pleural effusion is common in congestive heart failure. Occasionally a small amount of the fluid may extend into an interlobar fissure from the general pleural space.[1] However, interlobar effusion may occur without any fluid in the pleural cavity. Only 14 such instances are found in a review of the literature.[1, 2, 3, 4, 5, 6, 7, 8, 9, 10] The following case is reported to illustrate this unusual finding.

Case Report

A. N., a white male, aged 59, was first admitted to the hospital on October 13, 1942, complaining of severe shortness of breath, cough and moderate epigastric pain. He was well until May, 1942, when effort dyspnea, orthopnea, cough, and ankle edema first appeared. The symptoms steadily increased in severity. Paroxysmal dyspnea and bouts of epigastric pain were present for one month before admission.

On physical examination the patient appeared dyspneic and slightly cyanotic. The respiratory rate was 26. The temperature was 98° F. The jugular veins were distended. The heart was found to be enlarged on percussion. The apical impulse was in the anterior axillary line in the sixth interspace. The rhythm was regular and the rate 140. A soft systolic and a diastolic murmur were present over the mitral area. The systolic blood pressure was 170 and the diastolic 110. Moist râles were present at the bases of both lungs. The liver was enlarged and tender. There was moderate edema of the feet and legs.

Laboratory Examination. The red blood cell count was 3,910,000 and the hemoglobin 80 per cent. The white cells numbered 5,300, of which 75 per cent were polymorphonuclears, 19 per cent lymphocytes, and 6 per cent monocytes. The urine contained a trace of albumin and the specific gravity was 1.023. The non-protein nitrogen of the blood was 41 mg. per 100 c.c. The blood Wassermann and Kahn reactions were negative.

The electrocardiogram revealed a normal sinus rhythm, depressed ST_1, inverted T_1, a diphasic T_2, elevation of ST_4, and moderate left axis deviation.

A flat plate of the chest taken at a distance of six feet showed marked enlargement of the heart, slight clouding of both lung bases, and a sharply circumscribed shadow of increased density on the right side at the level of the interlobar fissure (figure 1). It measured 4 by 4 cm. On physical examination it was impossible to obtain any abnormal signs over the region comparable to the shadow.

Course in Hospital. The patient received 3 grains of digitalis daily between October 13 and October 26 inclusive. Orthopnea, cough, paroxysmal dyspnea, edema, and recurrent epigastric pain persisted for one week. At the end of this time, there was moderate diuresis and a gradual disappearance of the signs and symptoms of congestive failure. On October 27, a second roentgenogram revealed that the shadow previously noted on the right side had disappeared leaving a slight thickening of the interlobar pleura between the upper and middle lobes of the lung (figure 2). The patient was discharged on November 18, 1942, free from symptoms except for slight effort dyspnea.

The patient was readmitted to the hospital on November 15, 1943, with severe dyspnea, cough, and slight edema of the lower extremities of three weeks' duration.

* Received for publication September 1, 1944.
From the Medical Service of the Montefiore Hospital, Pittsburgh, Pennsylvania.

Physical examination revealed basal râles and enlargement of the liver. The systolic blood pressure was 152 mm. Hg and the diastolic 114 mm. Hg. The heart rate was 140 and the rhythm regular. Soft systolic and diastolic murmurs were present at the mitral valve area.

On November 15, a roentgenogram of the chest revealed a shadow in the interlobar space on the right side similar to that of the first admission (figure 3).

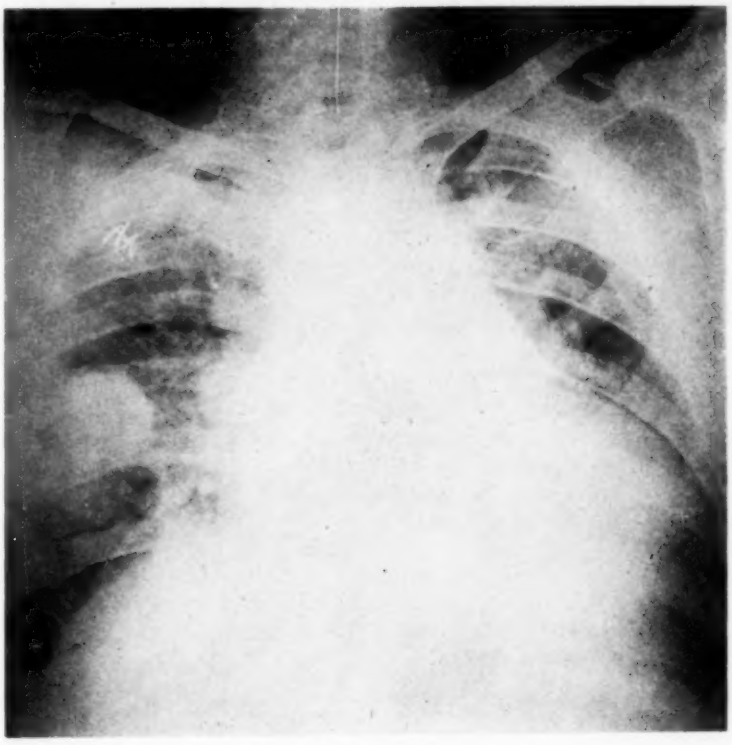

FIG. 1. Roentgenogram of chest, October 21, 1943, shows circumscribed shadow of interlobar effusion in the right chest.

Between November 15 and November 29 the patient received 9 grains of aminophylline daily without influencing the degree of heart failure. Roentgen examination on December 1 revealed no change in the size of the shadow. Eighteen grains of digitalis were administered between December 1 and December 4 together with 45 grains of ammonium chloride daily. Two c.c. of salyrgan were injected intravenously on December 4 and December 7 respectively. Following each injection the patient passed about 3,000 c.c. of urine. This was associated with disappearance of the signs and symptoms of heart failure. On December 8 a roentgenogram revealed a marked reduction of the shadow in the right chest (figure 4). The patient was discharged on December 23, 1943.

Anatomy. In order to understand the nature of this condition with its resultant clinical and roentgenological picture, an understanding of the anatomy of the interlobar fissures is important. The left lung is divided into two lobes by a single fissure. It begins dorsally about 5 cm. below the apex, about the level of

the third rib, and extends downward and ventrally to the diaphragmatic surface of the lung. The right lung is divided into three lobes by two fissures. The main fissure is similar in its position to the fissure in the left lung. It separates the lower lobe from the middle and upper lobes. The other fissure begins in the main fissure on the dorsal part of the lung, and extends ventrally, ending at the level of the fourth rib. It separates the middle from the upper lobe of the lung.[6]

Etiology. The serous type of interlobar effusion is usually due to a tuberculous infection of the lung; the purulent type is usually due to pneumonia. Other

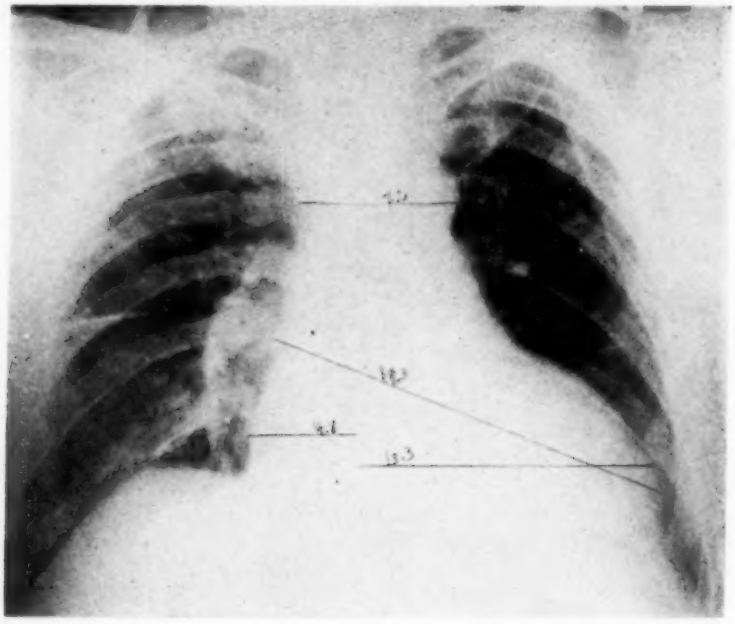

FIG. 2. Roentgenogram of chest, October 27, 1943, shows disappearance of interlobar effusion in the right chest.

less common causes of interlobar effusion are infections through the chest wall, and metastases through the blood or lymph stream from a distant focus of infection, such as tonsillitis, scarlet fever, puerperal infection, subphrenic abscess, etc.[11] Rarely interlobar serous effusion may be due to passive congestion as a result of heart failure.[1, 2, 3, 4, 5, 6, 7, 8, 9, 10]

Pathology. Necropsy of several reported cases of interlobar effusion associated with heart failure showed that fluid collected in the interlobar space because of either local adhesions [9] or because of an adhesive pleurisy which obliterated the entire pleural cavity with the exception of the small space between the lobes of the lung.[4, 7] The cause of the adhesions was a healed tuberculous lesion of the lung in one case [9] and unknown in the others.[4, 7]

Clinical Picture. It is interesting to note that in almost all of the reported cases there was no history of past pulmonary or pleural infection to explain the presence of pleural adhesions.

The etiology of the heart disease in the reported cases was hyperthyroidism in one,[8] syphilis in one,[9] rheumatic fever in one,[1] coronary artery disease with or without arterial hypertension in five,[1, 6, 7] calcification and stenosis of the aortic valve, probably degenerative, in one,[4] and pericarditis of unknown etiology in one case.[5] It is clear that interlobar effusion may be associated with any type of heart disease, and that the prerequisites for its development are congestive heart failure in a patient with an antecedent, adhesive pleurisy.[7]

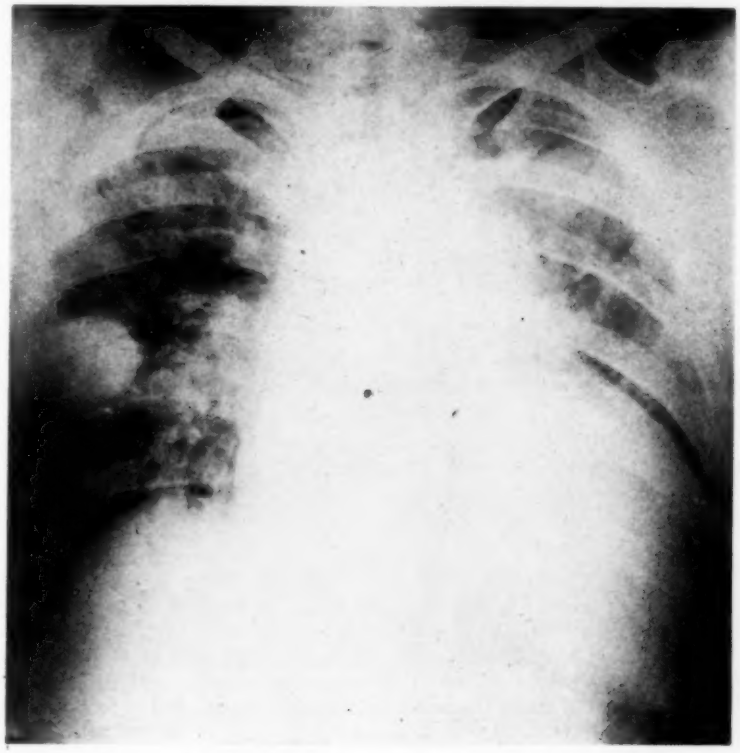

FIG. 3. Roentgenogram of chest, November 15, 1943, shows shadow in the right chest similar to that of one year ago when the patient was in congestive failure.

Clinically, it is impossible to recognize this condition because there are no characteristic signs or symptoms. The symptoms are due to congestive failure or to the underlying heart disease or to both. The amount of fluid is usually too small to produce symptoms or abnormal physical signs. Localized dullness and diminished breath sounds may occur in unusual instances [9] and suggest the possibility of this condition, but the diagnosis rests upon roentgen examination of the patient.

In all of the reported cases, as in our case, the effusion appeared on the right side, probably owing to the fact that fluid usually collects on this side in congestive failure.

Roentgenogram. Interlobar effusion produces a characteristic roentgen shadow. The location of the shadow depends upon the site of the fissure, and

upon what part of the fissure is occupied by fluid.[9] The size and shape of the shadow will depend upon the amount of fluid present and upon the degree of compression of the adjacent lung. Interlobar effusion usually causes a dense, sharply demarcated, homogeneous shadow. It may be round, oval, spindle-, wedge- or band-shaped.[1, 6] The margins are sharp unless there is thickening of the adjacent pleura or disease in the adjacent lung.

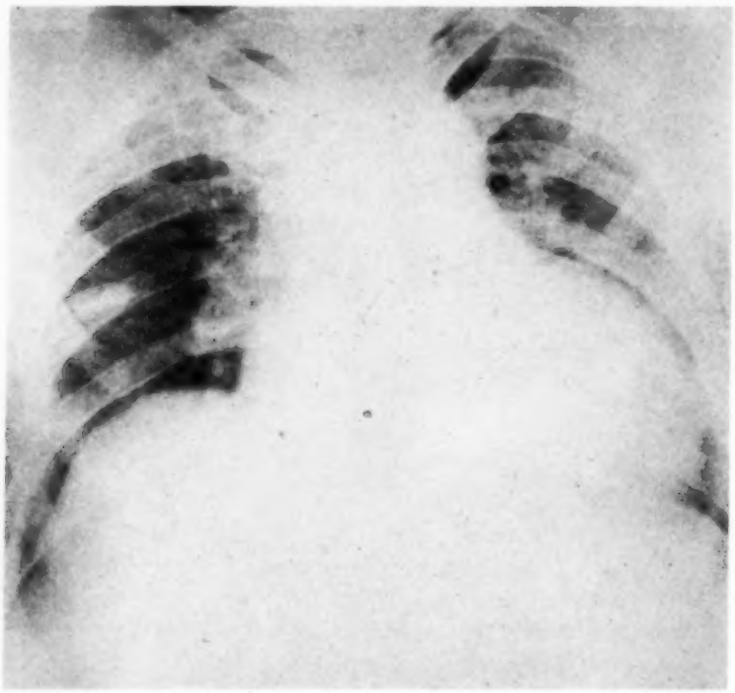

FIG. 4. Roentgenogram of chest, December 8, 1943, shows a marked reduction of the shadow in the right chest following the administration of diuretics.

Diagnosis. The roentgen shadow of interlobar effusion may simulate the appearance of interlobar empyema or of bronchiogenic carcinoma, metastatic neoplasm, pulmonary infarction, pneumonia, gumma or a localized caseating lesion situated in the region of the interlobar septum.[6] The differential diagnosis will depend upon (1) the general clinical picture of the patient, (2) careful roentgen examination, and (3) the response to therapy.

A lateral view of the chest may be necessary in differentiating an intrapulmonary lesion from interlobar effusion. The lateral view will show that a part of the lobe is involved with the lesion ending at the interlobar septum.[6]

Interlobar effusion due to heart failure will diminish or disappear shortly after the administration of a mercurial diuretic or an adequate amount of digitalis. This change in the shadow coincides with diuresis. On the other hand, the shadow may reappear with the reaccumulation of fluid, or with additional attacks of congestive heart failure. In one reported case the shadow recurred and sub-

sided four times.[4] The shortest interval between the initial attack and recurrence was 20 days,[4] the longest eight years.[7]

In many of the reported cases, as in our case, the roentgenogram revealed a thickened pleura on the side of effusion, suggesting obliteration of the pleural space.[1, 4, 7] In one case thickening of the pleura was indicated by the difficulty of performing thoracentesis.[7] Interlobar effusion may be recognized by tapping the chest,[9] but this procedure is usually unnecessary since the diagnosis may be made simply by the administration of an effective diuretic.

Conclusions

Interlobar pleural effusion may be a manifestation of congestive heart failure. The condition is due to the occurrence of congestive failure in a patient with an old adhesive pleurisy. The diagnosis rests on finding roentgenographically a dense, sharply circumscribed shadow in the region of an interlobar fissure which disappears following the administration of a mercurial diuretic or digitalis. The shadow is apt to reappear with the reaccumulation of fluid in the body.

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HYPERTENSION CAUSED BY RENAL INFARCTION *

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Of the numerous experimental investigations as to the pathogenesis of essential hypertension, the work of Goldblatt [1] is beyond doubt the most out-

* Received for publication July 20, 1944.
From the Medical Department of the Fairmount Hospital, Jersey City, N. J.

standing. In a classical experiment he produced hypertension in the dog by constriction of one or both renal arteries with a silver clamp, with a resultant decrease in the blood flow through the kidney. These experiments have been repeated by other investigators with the same result. It is believed that the diminution in renal flow produces hypertension by the secretion of a pressor substance into the blood by the ischemic kidney. Since then a number of reports have appeared in the literature describing instances of unilateral infections of the kidney causing hypertension. Thus, Butler [2] reported two cases of unilateral pyelonephritis with hypertension in children in whom nephrectomy was followed by the return to normal blood pressure. Barker and Walters [3] reported five similar cases in ages ranging from 7 to 52 years. Richards [4] reported a case of unilateral renal tuberculosis associated with hypertension with a drop of blood pressure and relief of symptoms following the removal of the diseased kidney.

More akin to the Goldblatt experiment are the reports of cases in which an impediment to the flow of blood caused by a narrowing of the renal arteries has been responsible for the coexisting hypertension. A case of hypertension caused by constriction of the renal arteries by a lymphosarcoma was reported by Blatt and Page.[5] Persistent hypertension in a five-year-old child with an aneurysm of the left renal artery was described by Howard, Forbes and Lipscomb.[6] Koons and Ruch [7] reported a case of hypertension in a seven-year-old girl in whom a Wilms' tumor caused a compression of the renal artery with a relief of the hypertension following the removal of the diseased kidney. Hoffman [8] reported a case in which a syphilitic saccular aneurysm with compression and narrowing of the left renal vessels was accompanied by hypertensive vascular disease.

There are two reports in the literature describing instances of renal infarction as a cause of hypertension. The first report is by Prinzmetal, Hiatt and Tragerman [9] describing a case in which hypertension resulted from bilateral renal infarction. They showed that perfusates from the infarcted kidney of a patient with hypertension contained a pressor substance similar to that which is found in the ischemic kidneys of animals with clamped renal vessels. The second report is by Fishberg [10] who described four cases in which embolization of one or both renal arteries was followed by a rise in arterial tension.

However, the embolization in these five cases occurred at the time, or shortly after, they came under observation, so that an individual predisposition or a preexisting hypertension could not be ruled out. The purpose of this report is to describe a case of hypertension caused by renal infarction in a patient who was under observation over a period of 12 years before embolization occurred. During this period hypertension was never noted. Furthermore, the patient recovered with a return to normal blood pressure which has remained normal two years following the infarction.

Case Report

A. M., single, white, female, aged 43 years, was admitted to the Fairmount Hospital on February 21, 1942, because of severe pain in the right loin and the right lower quadrant of the abdomen.

Past History. She had rheumatic fever at the age of 12 and again at the age of 16. She was first seen on October 29, 1930, because of palpitation and slight dyspnea on exertion. Examination disclosed mitral stenosis and insufficiency and

an enlarged heart. The blood pressure was 130 mm. Hg systolic and 76 mm. diastolic. There was no change in her cardiac status until December 10, 1939, when auricular fibrillation was noted. She was digitalized and felt well on a maintenance dose of digitalis until her present illness. The blood pressure was normal throughout this period.

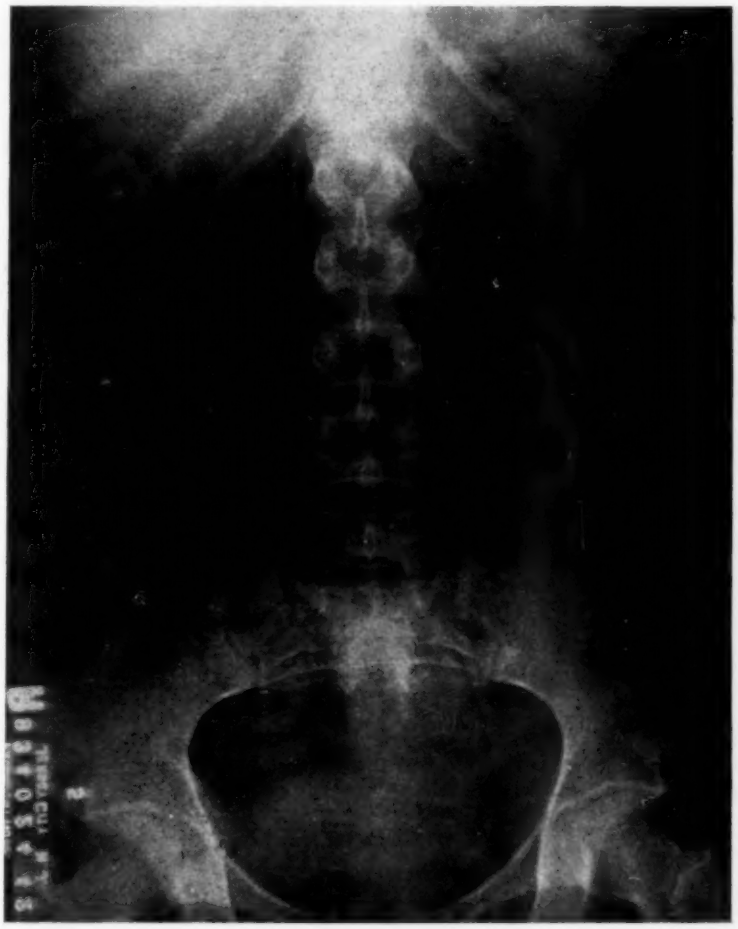

FIG. 1. Intravenous urogram showing no function of the right kidney and normal function of the left kidney.

Present Illness. Twelve hours before admission, the patient suddenly felt severe pain in the right loin and the right lower quadrant of the abdomen. This was followed in a half-hour by vomiting. The pain, which was described as severe and cutting in character, began anteriorly and radiated to the right costovertebral region. It did not radiate to the perineum. At times she had pain all over the abdomen. For the first eight hours there was complete anuria. This was followed by hematuria.

Physical examination revealed a well-nourished woman in apparent distress. The veins of the neck were distended. The heart was enlarged to the left. Systolic and diastolic murmurs were heard at the apex. The second pulmonic sound was louder

than the aortic and accentuated. The rhythm was totally irregular. The ventricular rate was 168; the pulse rate, 126. There were crepitant râles in the bases of both lungs. The abdomen was distended. The liver was felt three fingers'-breadth below the right costal margin. The spleen was not felt. There was no ascites. There was marked tenderness with spasm over the right side of the abdomen, particularly the

FIG. 2. Retrograde pyelogram showing no abnormality of the right pelvis and right ureter.

right lower quadrant. There was marked tenderness to percussion over the right costovertebral angle. There was no peripheral edema. The temperature was 103.4° F. The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic.

Laboratory. The urine showed a specific gravity of 1.030, a 4 plus albumin, many red cells and a few white cells. The blood count revealed: red blood cells 4,610,000, hemoglobin 90 per cent, white blood cells 25,000. Differential count:

Polymorphonuclears mature 72.5 per cent, band forms 6.5 per cent, small mononuclears 11.5 per cent, large mononuclears 2 per cent, transitionals 7.5 per cent. A blood examination on January 22 showed non-protein nitrogen 67 mg. per 100 c.c. and sugar 130 mg. per 100 c.c.

Date	Laboratory data
1/21	Urine: 4 plus alb., many red cells, few white cells.
1/22	Non-protein nitrogen 70; leukocytosis.
1/23	Excretory urogram: left kidney, normal function; right kidney, no function.
1/26	Urine: 3 plus alb., many red cells, few white cells.
1/28	Retrograde pyelogram: no abnormality of the right pelvis and right ureter.
2/2	Non-protein nitrogen 70; urine: 3 plus alb., many red cells.
2/4	Excretory urogram: no function right kidney.
2/14	Non-protein nitrogen 36; urine: 2 plus alb., few red cells.
2/19	Urine: 1 plus alb., occasional red cell.
2/20	Excretory urogram: normal function both kidneys.

Roentgen-ray examination of the chest on January 22 showed the heart to be greatly enlarged and of the mitral type. There were haziness and increased density throughout both lung fields.

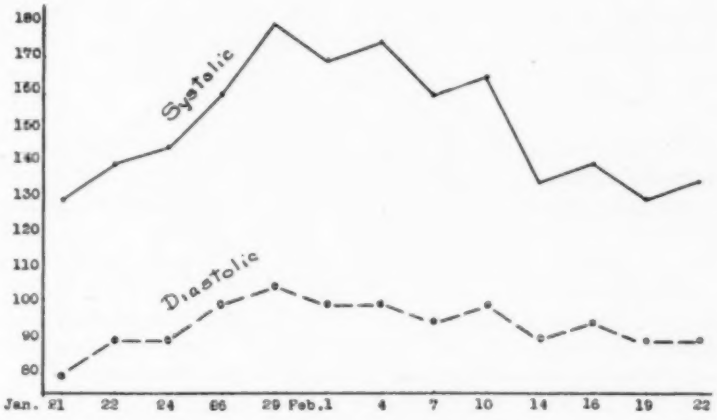

FIG. 3. Graph showing elevation of arterial pressure following renal infarction, with subsequent return to normal.

The electrocardiogram showed auricular fibrillation; ventricular extrasystoles depression of ST_2 and ST_3; inverted T_2, T_3 and T_4; and right axis deviation.

A flat plate of the abdomen did not reveal any abnormalities.

Excretory urogram (figure 1) performed on January 23 disclosed normal visualization of the left urinary tract but no visualization of the right side.

Cystoscopy was performed on January 28. There was prompt flow of indigo carmine with good concentration in five minutes on the left side, but no flow on the right side.

A retrograde pyelogram (figure 2) did not show any abnormalities of the pelvis or ureter of the right kidney.

Course. The pain was severe for the first two days and then it began to subside. The tenderness and spasm also became less marked on the third day. The temperature ranged from 101° to 103.4° F. for the first five days and then began to subside, but there was a low grade fever for the following 15 days. On the sixth day following the infarction, the blood pressure rose to 160 mm. Hg systolic and 100 mm. diastolic.

The subsequent blood pressure readings are shown in the accompanying graph (figure 3).

On February 2 the non-protein nitrogen was 70 mg. per 100 c.c. An intravenous urogram on February 4 still showed no function on the right side. On February 16 the non-protein nitrogen was 36 mg. per 100 c.c. An excretory urogram on February 20 showed normal function of both kidneys. The patient was discharged improved on February 22. The blood pressure has remained normal in the two years following the infarction.

Comment

A diagnosis of renal infarction was made on the basis of sudden severe pain in the right loin and right lower quadrant of the abdomen, followed by hematuria in a patient with mitral stenosis and auricular fibrillation. This diagnosis was confirmed by an intravenous urogram showing no function in the right kidney, and by a retrograde pyelogram showing no abnormalities in the pelvis or ureter of the same side. On the sixth day following the infarction, the blood pressure became elevated to 160 mm. Hg systolic and 100 mm. diastolic, and reached 180 mm. Hg systolic and 106 mm. diastolic on the twelfth day. The blood pressure remained elevated for 21 days and then returned to its previous level. The function of the kidney returned to normal at the same time.

Summary

A case is presented with mitral stenosis and auricular fibrillation in which an embolus in the right kidney resulted in elevation of the arterial pressure. The blood pressure returned to normal with the disappearance of symptoms of renal infarction.

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SPONTANEOUS HEMOPNEUMOTHORAX: REPORT OF A CASE OCCURRING IN A SOLDIER *

By JOHN FRANKLIN, Capt., M.C., A.U.S., *Hunter Field, Georgia*

THE true incidence of spontaneous hemopneumothorax is unknown. Whereas the literature contains reports of sporadic cases, many cases are not reported, and many cases are misdiagnosed as hydropneumothorax, when roentgen evidence of fluid alone is accepted without the benefit of a diagnostic thoracentesis. In 1937, Hopkins [1] collected 43 cases from the literature and reported three cases of his own. Hartzell [2] in 1942, reported 40 selected cases from the literature and three cases observed at Cleveland City Hospital during the preceding 10 years. The apparent rarity of this complication of spontaneous pneumothorax prompts me to report the following case.

CASE REPORT

M. A. H., aged 23, Private First Class, United States Army, was admitted to the Station Hospital, Hunter Field, Georgia, on August 27, 1943, complaining of severe upper abdominal and right chest pain. The admitting diagnosis was acute cholecystitis.

Family History and Past History. The patient's mother had pulmonary tuberculosis during the period of the patient's adolescence. The patient was employed as a potter for three years during after-school hours from 1937 to 1940. The atmosphere was very dusty and he coughed frequently and experienced frequent epistaxes. Two years before admission he had an attack of right pleuritic pain lasting one week which was associated with a slight dry cough, but no chills or fever. During the two months prior to admission the patient complained of pain at the left costal margin, exaggerated by exercise. His dispensary record carried the diagnosis of intercostal neuralgia. No chest roentgenogram was taken. He had been thin since birth but capable of normal physical exertion. However, during the previous eight months of service this soldier felt under par and fatigued easily. The chest roentgenogram upon induction one year prior to admission was reported clear. As the soldier was on limited service because of frequent attacks of migraine headache, he was not subject to strenuous physical exertion.

Present Illness: The present illness began one week prior to admission when the patient developed a recurrence of pleuritic pain over the right anterior chest, similar to the pain noted two years previously. Pain was so severe that he sought relief on sick call. Physical examination at this time revealed the chest and heart to be normal. No roentgenogram of the chest was made. The night of admission, the patient experienced severe pain over the right anterior chest which radiated to the right upper abdominal quadrant and to the right shoulder. Breathing became shallow and difficult and shortly after this he became nauseated and vomited several times.

Physical Examination. Temperature 100° F. Pulse 110. Respirations 30. Blood pressure 90 mm. Hg systolic and 70 mm. diastolic. The patient appeared acutely and seriously ill. There was a marked sallow yellow color to the skin and pallor of the mucous membranes. Respirations were rapid, labored and shallow and the patient held his right side as he breathed. There was no cough. He was quite thin and underweight.

Significant findings were limited to the chest and abdomen. The trachea was markedly displaced to the left. There was an inspiratory lag which involved the entire right chest. The intercostal spaces on the right were distended. There was

* Received for publication June 10, 1944.

increased precordial activity and a prominent cardiac impulse could be seen in the fourth and fifth left interspaces at the anterior axillary line. The percussion note over the right chest was hyperresonant and the normal hepatic dullness was obscured in the supine position. In the upright position flatness to percussion was present from the eighth rib down posteriorly on the right. Breath sounds, vocal and tactile fremitus were absent over the entire right chest. The heart sounds were of good quality. There was a loud high pitched systolic murmur over the entire precordium. The abdomen was held rigidly and deep palpation was resisted. The liver could be percussed two fingers' breadth below the costal margin. There was exquisite right upper quadrant tenderness.

Laboratory Results. A chest roentgenogram confirmed the original clinical impression of a hydropneumothorax. There was complete collapse of the right lung, with a fluid level approximating the eighth rib posteriorly. The trachea and heart were displaced to the left and herniation of the mediastinum had occurred (figure 1).

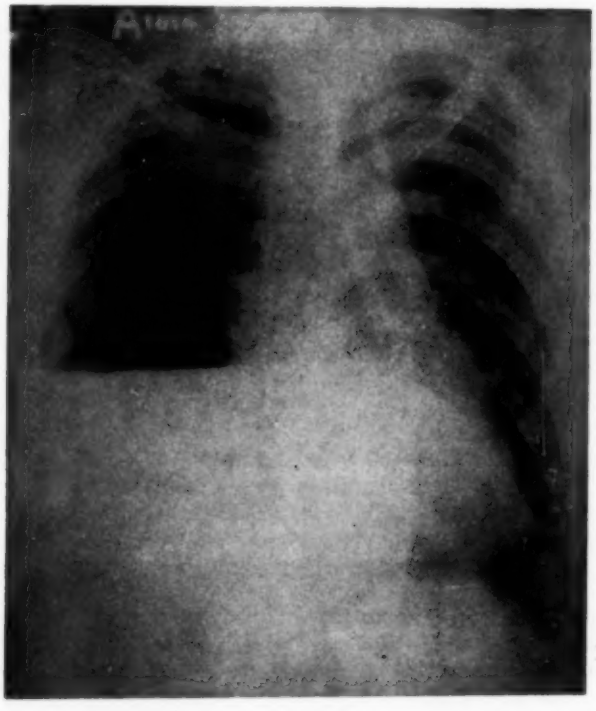

FIG. 1. Chest roentgenogram taken on admission showing complete collapse of the right lung, a fluid level approximating the eighth rib in the posterior axillary line, displacement of the trachea and heart to the left, and herniation of the mediastinum and right lung due to the pressure of the air in the right pleural cavity.

A diagnostic thoracentesis resulted in the removal of air and blood under pressure. Approximately 700 c.c. of air were removed and 25 c.c. of blood with a red cell count of 3,160,000 and a white cell count of 6,900. The fluid was sterile. Smear, culture and guinea pig inoculation failed to reveal the presence of acid fast bacilli. Pleural pressure was not recorded. The patient's red cell count was 4,310,000, with a hemoglobin of 11.5 grams and a white cell count of 15,650. The differential revealed a shift to the left. The urine was normal.

Course and Treatment. The patient experienced immediate relief of his respiratory distress with the removal of air from the right chest. There was a noticeable shift of the mediastinum toward the midline following this procedure (figure 2A). The incipient shock was treated by the administration of intravenous glucose and saline followed by two 500 c.c. transfusions of Type B blood. The blood pressure rose to 105 mm. Hg systolic and 70 mm. diastolic where it remained. Morphine was required only during the first 24 hours to control the patient's pleural pain and anxiety. The liver receded above the costal margin and the right upper quadrant tenderness subsided with the relief of the tension pneumothorax. With the return of the mediastinum to the midline, the systolic murmur disappeared. A pleural pressure reading at this time indicated a pressure of 0 to + 5 and 200 c.c. air were removed to bring the pressure to atmospheric level. At no time subsequently did the pleural pressure rise above + 5 and sufficient air was removed from time to time to maintain the mean pressure at 0.

On the second hospital day the patient's temperature rose to 104° F. and for two days thereafter ranged between normal and 102° F. Thereafter the fever fell by lysis and was normal by the ninth hospital day. Pulse and respirations became normal during the same period.

On alternate days beginning on the third hospital day, four thoracenteses resulted in the removal of a total of 2,700 c.c. of grossly bloody fluid showing a decreasing red cell count from 3,160,000 to 510,000 and a rising relative eosinophile count from 18 per cent to 43 per cent. The fluid white cell count never rose above 9,850. In each instance the fluid obtained was sterile. Search for acid fast bacilli was made and none was found. Culture and guinea pig inoculations were done by the Fourth Service Command Laboratories and all results were negative for tuberculosis. The patient's originally high blood count probably reflected dehydration as, following the administration of intravenous fluid and despite two transfusions, the red cell count fell to 3,780,000 and the hemoglobin to 10.5 gm. This gradually rose to normal with the stimulus of a high caloric and high vitamin diet and supplemental iron. At no time did the patient reveal clinical icterus.

Progressive chest roentgenograms (figure 2) showed a decreasing fluid level and progressive reëxpansion of the right lung. The lung at the last examination had entirely reëxpanded, the costophrenic angles were clear, and there were no parenchymal changes to suggest pulmonary tuberculosis. An intradermal test using second test strength (0.005 mg.) P.P.D. was negative after 48 hours. The patient was considered cured and returned to duty after a period of convalescence.

Discussion

Although the equilibrium of increased pleural pressure and lowered blood pressure is probably effective in controlling bleeding, the respiratory embarrassment and incipient circulatory collapse occasioned by the acute and massive loss of blood in this case, plus the marked mediastinal displacement, forced us to relieve the pleural tension and replace the blood loss. It is difficult to estimate accurately the acute blood loss. A total of 2,700 c.c. of bloody fluid was removed containing both serum and whole blood. The red cell count of the original fluid removed was comparable to that of the systemic blood discounting the effect of dehydration from protracted vomiting as well as the loss of blood volume. At the time of the first thoracentesis there was no clinical or roentgenographic evidence of continued bleeding. As the patient's body weight was about 57 kilograms, the blood lost was probably in excess of 30 per cent of his blood volume estimating the latter at 4¾ liters. The acute loss of 30 per cent of one's

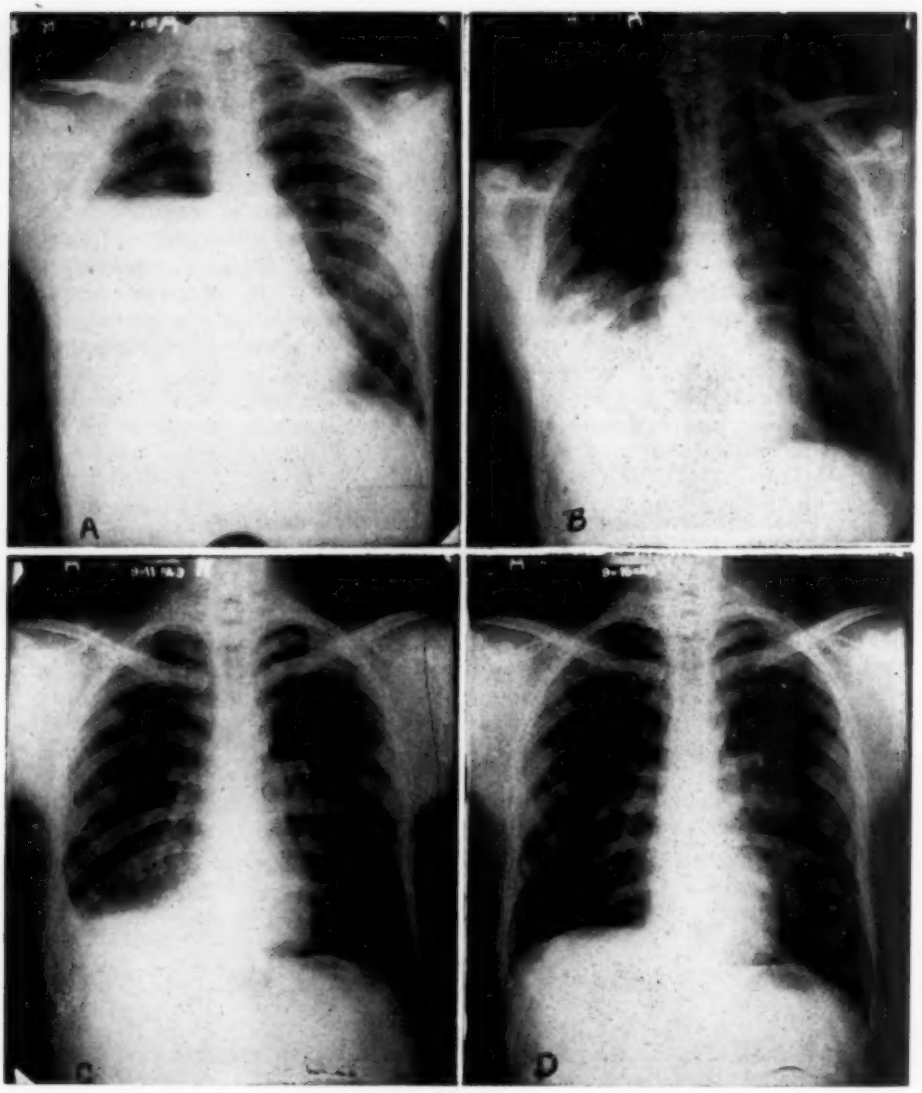

FIG. 2. (A) Portable roentgenogram taken on the second hospital day following the removal of 1100 c.c. of air from the right pleural cavity showing a decided shift of the trachea, heart and mediastinum toward the midline with a consequent displacement of the fluid and rise in the fluid level. (B) Portable roentgenogram taken on the fifth hospital day after the removal of 1,200 c.c. of grossly bloody fluid showing incomplete reëxpansion of the right upper lobe and a fall in the fluid level. The heart and mediastinum are centrally located. (C) Roentgenogram taken on the sixteenth hospital day showing complete re-expansion of the right lung except at the extreme right apex where an irregular radiolucent area suggests the presence of an emphysematous bleb. The right costophrenic sinus and diaphragm are still hazy. (D) Roentgenogram taken on the twenty-first hospital day showing complete reëxpansion of the right lung and complete reabsorption of fluid. The area previously described at the right apex now appears to be only thickened pleura. There are no parenchymal changes to suggest active pulmonary tuberculosis.

blood volume is considered the limit beyond which the physiologic mechanisms of replacement fail. Consequently, the replacement of fluid and whole blood was indicated.

This case falls into the category of those variants in the clinical picture of hemopneumothorax in which the signs and symptoms are referred to the abdomen. The presence of right upper quadrant pain and tenderness, radiation of pain to the right shoulder, nausea and vomiting, and sallow yellow pallor suggestive of icterus was indeed confusing. It is interesting to note that the admitting diagnosis was acute cholecystitis.

The pathogenesis of this instance of hemopneumothorax was not determined. Despite a strong family history of tuberculosis and a suggestive past history of chronic disease, no evidence of tuberculosis could be found. The work of Kjaergaard,[3] Hamman,[4] Kirshner [5] and others offer many explanations for spontaneous pneumothorax. The presence of ruptured emphysematous blebs has been observed in several cases of hemopneumothorax which have come to the autopsy table, and pleural bullae also have been demonstrated radiologically. These constitute a ready source for the escape of air into the pleural cavity and one needs but postulate the presence of a valve vesicle to explain a tension pneumothorax. The source of the bleeding may well be from the ruptured vesicle itself as Mazzei and Pardal [6] have shown these bullae to be richly vascularized. A more likely possibility is that bleeding results from an adhesion torn by the traction of the collapsing lung. Adhesions are frequent [7] and this source of bleeding is relatively common in artificially induced pneumothorax.

Summary

A case of benign spontaneous hemopneumothorax has been presented in which the presenting symptoms and signs were referred to the abdomen. The treatment and probable etiology have been discussed.

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MULTIPLE FRACTURES OF RIBS BY COUGH: REPORT OF A CASE *

By OSCAR SWINEFORD, JR., M.D., F.A.C.P., and JOHN MCKINNON, M.D.,
University, Virginia

FRACTURE of one or more apparently normal ribs by cough was first described by Graves[1] in 1834. Tunis [2] found 25 cases in the literature in 1890. Atkinson,[3] Seilin,[4] Webb and Gilbert,[5] and Brewster [6] added seven cases. Halliwell,[7] Howson,[8] and Richardson,[9] each reported four such fractures in a single case. The report of Sabbione,[10] in Italian, was not read. Oechsli [11] found 12 cases in 2,000 patients with pulmonary tuberculosis, an incidence of 0.6 per cent. Richardson [9] found 20 cases in 1903 patients with tuberculosis. The incidence was 0.8 per cent in incipient, 2 per cent in moderately advanced, 6.5 per cent in far advanced cases. He thinks such fractures are much more common than is generally appreciated. He points out that they are usually small linear breaks which are not very obvious in roentgenograms until callus forms. The symptoms are those of pleurisy and they occur in patients in whom pleurisy would be expected. He thinks bony decalcification due to tuberculosis is a contributory factor.

Fractures of ribs by cough have been found in association with "chronic bronchitis," asthma, foreign body in the larynx, and in pulmonary tuberculosis.

The following case is presented because it is the largest number of ribs fractured by coughing in a single individual, because there was no demonstrable evidence of decalcification nor of bone disease, and because the cough was due to simple bronchosinusitis and not to tuberculosis.

CASE REPORT

A 35 year old housewife had had repeated winter respiratory infections since adolescence. They had been particularly troublesome during the past four years. The usual respiratory infections began in November 1943. Several weeks later she had an acute pain in the left lower axillary area. This had the characteristics of a rather severe pleural pain. Roentgenograms showed no abnormalities in the chest, nor in the ribs, except some thickening of the bronchial markings. She continued to have remissions and exacerbations of the cough, low grade fever, and severe pleural type of pain.

Two weeks before admission, our first examination, she developed another severe cough with pain in the left lower chest increased by cough and respirations. No abnormal signs were heard in the chest. She began treatment for purulent sinusitis of the antra, by lavage, on April 14, 1944. She had had a mild fever for several days. The pain subsided in a few days but the cough persisted.

Three days before admission on April 24, 1944 she had another episode of severe pleural pain in the right lower chest. In the hospital she was found to be very poorly nourished. She was coughing frequently and vigorously. Each cough and each inspiration produced severe right lower chest pain. The respiratory motions were splinted on the right. The eighth right rib area was quite tender. A loud pleural rub was heard under the area of tenderness.

* Received for publication July 20, 1944.
From the Department of Internal Medicine, University of Virginia Medical School, Charlottesville, Va.

Roentgenogram of the chest showed transverse fractures of the left sixth and seventh and of the right eighth ribs with callus. In addition the left eighth and the right tenth ribs were fractured incompletely near the mid-axillary lines. The bronchial markings in the bases were quite heavy suggesting either severe bronchitis or early bronchiectasis. Roentgenograms of the sinuses showed pansinusitis. There was no evidence of decalcification of the skull, ribs nor vertebrae. Chest films made in 1940 and 1930 were available for comparison. There was no history of injury. The serum calcium was 10 mg. per 100 c.c., blood phosphorus 4.4 mg. per 100 c.c., serum phosphatase 4.4 units. The plasma total protein was 6.5 gm. per 100 c.c. The tuberculin test was and had been repeatedly negative. Fasting plasma vitamin C was 1.2 mg. per 100 c.c. The sternal bone marrow showed no abnormalities. A biopsy of the right fourth rib showed normal cancellous bone.

On June 5 she fractured another rib. Films of the chest June 6 showed (figure 1) six calluses and one linear fracture. Another fracture on June 9 made a total of eight fractures.

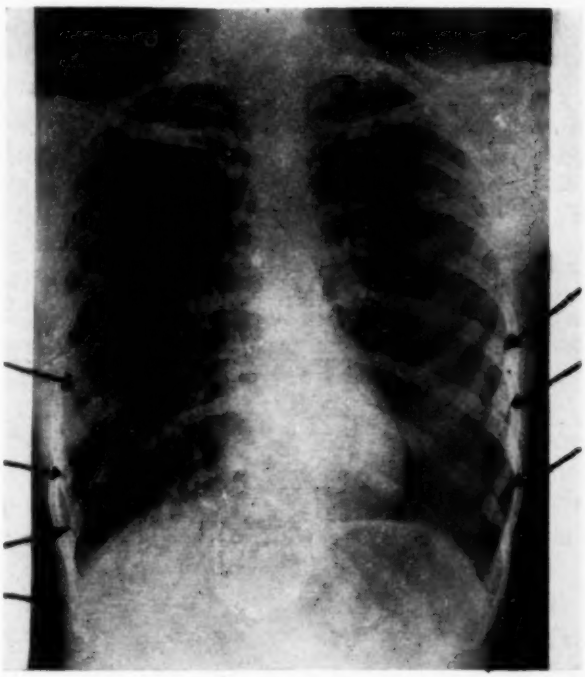

FIG. 1. Arrows point to the rib fractures with callus formation and to the linear fractures.

Roentgen therapy plus lavage of the antra produced marked improvement in the cough and in the sinuses. The aptra washed clear and were clear in a roentgenogram on June 6, 1944. She had had about 150 multi-vitamin capsules in six weeks when the seventh and eighth fractures occurred.

SUMMARY AND CONCLUSIONS

A case is reported in which eight apparently normal ribs were fractured by cough within six months. The patient had bronchosinusitis. She was very thin. There was no evidence of tuberculosis. Multi-vitamin therapy plus milk

in abundance did not prevent additional fractures. The symptoms were indistinguishable from pleurisy. A pleural rub was heard with only one of the last four fractures. Moderate tenderness over the fracture was the most suggestive physical sign. Until callus forms only careful search of roentgen films may disclose the usually linear breaks. Fractures of ribs by cough are probably more frequent than is realized.[9] They must be thought of whenever there is pleuritic pain plus tenderness. The literature is reviewed.

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EDITORIAL

IMMUNITY AND IMMUNOLOGICAL REACTIONS IN MUMPS

THE etiological agent in mumps was first isolated by Johnson and Goodpasture [1] and by Findlay and Clarke.[2] These investigators were able to reproduce the disease in monkeys (Macacus) by injecting into the parotid duct saliva from human cases of mumps obtained during the first or second day of the disease. They demonstrated that the agent was a filtrable virus which was present in the saliva of the patients and in the tissue of the infected parotid glands of the monkeys. They also found that after recovery the monkeys were immune to reinoculation. Until recently, however, little was known as to the mechanism of the immunity, nor were there available specific methods of diagnosis or procedures which would determine immunity or susceptibility in human beings.

Although mumps is usually a mild infection with a very low mortality, it is highly contagious and spreads rapidly when introduced into closed communities of susceptible individuals such as schools or military establishments. Under these conditions it causes a serious, if temporary, loss of manpower, particularly in those cases with disabling complications like orchitis or meningoencephalitis. In such situations effective measures of control would be of great practical value. Recent work by Enders, Kane and their associates has contributed materially to this end. These investigators [3] reproduced the disease regularly in monkeys by the method used by Johnson and Goodpasture. In parotid glands removed by operation a few days after inoculation they demonstrated the presence of active virus, often in high concentration, even in animals in which little or no enlargement of the parotids was evident clinically. They were unable to demonstrate the virus in any other tissues or organs of the infected monkeys, nor to cause infection or demonstrate multiplication of the virus after inoculation by any other route. Attempts to demonstrate virus-neutralizing activity in the pooled serum of convalescent human cases gave somewhat equivocal results. In three experiments virus was demonstrated by complement fixation tests in the parotid glands of the "protected" animals, but the titer was much lower than in the controls. It is probable, therefore, that some neutralizing power was present.

By using suspensions of infected parotids as antigen, however, they were able to demonstrate complement-fixing antibodies in the serum of infected monkeys after recovery in practically every case. In some animals it could

[1] JOHNSON, C. D., and GOODPASTURE, E. W.: Investigations of etiology of mumps, Jr. Exper. Med., 1934, lxix, 1–19.

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be demonstrated (in low titer) within a few days after inoculation, and in most animals it was present in high titer by the end of the second week. After about one month the titer fell, but in some cases significant amounts remained after 10 to 21 months. No antibody was found in normal monkeys, but in a few cases antibody appeared in monkeys which had been in casual contact with infected animals, although no clinical manifestations of infection had been recognized.

By the same method these workers [4] demonstrated the regular appearance of complement-fixing antibody in the serum of human convalescent cases. In a few cases it appeared or was present in low titer at the onset of clinical manifestations of infection but increased markedly in titer during convalescence. In those cases which were tested early, it was absent before and (usually) at the onset of the disease, but reached high titers during the second and third weeks. This persisted in lower titer for months; in three of four cases tested it was present two years after the infection.

The reaction appears to be useful in the recognition of atypical cases of infection without obvious involvement of the salivary glands. In a study of 51 patients showing clinical manifestations of meningoencephalitis,[5] positive reactions were obtained in all of 17 cases which showed enlargement of the salivary glands. In 16 of the cases without involvement of the salivary glands, positive reactions were also obtained, whereas in 18 others, clinically indistinguishable, the reaction was negative, and some other etiological agent presumably was concerned.

In most normal individuals without a history of mumps, the complement fixation reaction was negative. It was also negative in all of a number of cases suffering from other types of infection. In some cases, however, a positive reaction was obtained although no previous attack of mumps was known to have occurred. Since all other available evidence indicates that the reaction has a high degree of specificity, it seems probable that these individuals had had an atypical or subclinical attack of the infection. That this may occur is indicated by observations on a laboratory worker who was handling mumps virus and whose complement fixation reaction, previously negative, became positive under observation, although there was no clinical evidence of illness.

Since it was found possible to destroy the infectivity of a virus suspension without loss of the antigenic power, this material could be used to determine the presence of cutaneous hypersensitivity in convalescent cases. In a preliminary study of a small group of normal individuals, intracutaneous injection of inactivated virus caused no reaction before infection or during the acute phase. The reaction became positive in all these cases during con-

[4] ENDERS, J. F., COHEN, S., and KANE, L. W.: Immunity in mumps. II. The development of complement-fixing antibody and dermal hypersensitivity in human beings following mumps, Jr. Exper. Med., 1945, lxxxi, 119–135.

[5] KANE, L. W., and ENDERS, J. F.: Immunity in mumps. III. The complement fixation test as an aid in the diagnosis of mumps meningoencephalitis, Jr. Exper. Med., 1945, lxxxi, 137–150.

valescence at intervals varying from one week to three months. The appearance of a positive reaction was also observed following an inapparent infection. The hypersensitivity in most instances lasted at least one and one-half to two years. There was no relationship between the presence of complement-fixing antibody in the serum and the cutaneous hypersensitivity. The latter appeared later in convalescence and in some cases at least persisted longer than the complement-fixing antibody. In a few cases, however, cutaneous hypersensitivity failed to develop or disappeared more quickly after an attack.

The possibility of active immunization from mumps was also investigated. Monkeys were injected subcutaneously with virus suspensions inactivated by means of formaldehyde, and two to four weeks later a suspension of infectious virus was inoculated into the parotid duct. The gland was excised five or six days later, and the occurrence of antigen, and its quantity if present, as determined by complement fixation tests, were used as criteria of immunity or susceptibility. In about two-thirds of the vaccinated animals antigen was either not demonstrable by the method used or was present in quantities significantly less than in unvaccinated controls. The authors concluded that the procedure is capable of conferring a substantial degree of immunity, and this conclusion seems valid, since the infecting dose was a large one, not well adapted to demonstrate lesser degrees of resistance.

The work which has been briefly reviewed indicates that the complement fixation reaction may have diagnostic value in identifying atypical cases of mumps without salivary gland involvement, and occasionally in differentiating mumps from other conditions causing enlargement of these glands. The reaction seems to be as highly specific, but subject to the same limitations in its interpretation, as are serologic reactions in other infections.

The immediate practical value of this work depends chiefly upon the reliability of these measures as aids in the epidemiologic control of the disease. Manifestly it would be highly important to have means of distinguishing immune and susceptible individuals, and if possible of immunizing the latter. Since the immunity following recovery from mumps is usually of long duration and high in degree, proof that an individual had passed through an attack would be strong presumptive evidence of resistance. The animal experiments reviewed suggest that these measures may serve this purpose, but definite conclusions can be drawn only from a study of human beings. Extensive studies along these lines have been undertaken, but at the time this review was written, only preliminary statements were available. In general, a positive complement fixation reaction or intracutaneous test seems to be strong presumptive evidence of immunity, although a few individuals who had shown positive reactions proved susceptible on subsequent exposure to the virus. Conversely, a negative reaction constitutes presumptive evidence of susceptibility. Exceptions also occur, however, and hypersensitiveness

may gradually disappear. It is not yet evident whether these exceptions are sufficiently frequent seriously to impair the practical value of the tests. Little can now be said regarding the immunization of human beings. The results obtained appear to be sufficiently encouraging to warrant the hope that an effective technic can be devised. One practical difficulty has been dependence on the parotid glands of monkeys as a source of virus. The other laboratory animals tested were insusceptible, and reported attempts to secure growth in tissue cultures and in developing chick embryos were unsuccessful. The final report of these studies will be of great interest.

REVIEWS

Penicillin Therapy Including Tyrothricin and Other Antibiotic Therapy. By JOHN A. KOLMER, M.D. 302 pages; 15 × 22 cm. D. Appleton-Century Co., New York. 1945. Price, $5.00.

This timely monograph is offered primarily as a clinical guide to the rational use of penicillin and as such is of interest to the physician and dentist. However, Dr. Kolmer describes authoritatively the laboratory aspects of the source, production, detection, and assaying of penicillin, and also its physical, chemical, and pharmacological properties. The antimicrobial activity of penicillin in vitro and in vivo is discussed in detail.

The author has summarized the literature which has accumulated concerning administration and dosage of penicillin, principles of penicillin therapy, and therapeutic effectiveness of penicillin in the prevention and treatment of various diseases. He has carefully evaluated the abundant data on antibiotic therapy and has presented it in a stimulating and concise manner compatible with present data and experience but at the same time raising questions to be answered by further experiment and clinical trial.

The author has used the term "antibiotic" in a restricted sense to mean "antimicrobial agents produced by living bacteria, yeast, molds and other plants" and has included a chapter on tyrothricin, gramicidin S, streptothricin, patulin and chlorophyll.

Each chapter represents a review of a large number of articles; for example, the chapter on "Antimicrobial Activity of Penicillin" includes 95 references. Yet this work is more than a critical review, because the author goes beyond the present familiar substances and suggests the rôle of future therapeutic agents, such as streptomycin and penicillin-like antibiotics, in the treatment of disease.

The book is recommended to the clinician, bacteriologist, and biological chemist as a reference work on the nature of penicillin and a practical clinical guide to penicillin therapy.

M. V. P.

Secretory Mechanisms of the Digestive Glands. By B. P. BABKIN, M.D., D.Sc., LL.D., F.R.S.C., Research Professor of Physiology, McGill University, Montreal, Canada; formerly Professor of Physiology, McGill University of Odessa, Russia and in Dalhousie University, Nova Scotia, Canada. 900 pages; 16 × 24 cm. Paul B. Hoeber, Inc., New York. Price, $12.75.

The purpose of the author in presenting this volume is, according to the preface, to describe the mechanisms involved in the regulation of the secretory activity of the principal digestive organs under normal conditions and to serve as a physiological introduction to the pathology and the clinical investigation of the secretory apparatus of the alimentary tract. The book is based primarily upon the animal experiments of the author but includes the findings of other investigators in order to present as unified a picture as possible of the present knowledge of secretory mechanisms. The clinical application of some of the experimental work is discussed. The first few chapters present general principles correlating structure and function of the secretory cells of the gastrointestinal tract. Photomicrographs and schematic drawings serve to illustrate the changes which take place during secretory activity and during the restoration to the presecretory phase.

Following the more general chapters, specific phases of the secretory mechanisms of the various organs are presented in great detail. Sixteen chapters are devoted to gastric and six to salivary secretion. Four chapters are given over to the hormones

of the intestinal tract. Besides the well established hormones, there is a discussion of the possible hormone effect of substances such as lipocaic and increten.

The advantages of the somewhat complicated Agren-Lagerlof procedure for obtaining samples for gastric analysis and the use of histamine, insulin and the usual test meals as stimuli for gastric secretion are discussed in a chapter on clinical applications. The author has pointed out the advantages to be gained by the use of each of these stimuli.

This volume contains a wealth of material which is readily available through an extensive subject and author index.

Paul B. Hoeber, Inc. has maintained its usual high standards in the production of the volume.

M. A. A.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Pulmonary Tuberculosis in the Adult. Its Fundamental Aspects. By MAX PINNER, M.D. 579 pages; 23 × 15 cm. 1945. Charles C. Thomas, Springfield, Illinois. Price, $7.50.

Revista "Universidad de Antioquia." No. 70. 339 pages; 24.5 × 17.5 cm. April and May 1945. Universidad de Antioquia, Medellin-Colombia.

Carbon Monoxide: Its Hazards and the Mechanism of Its Action. Public Health Bulletin No. 290. 257 pages; 23 × 15 cm. 1944. Federal Security Agency—United States Public Health Service, Washington, D. C.

Arquivos da Policia Civil de São Paulo. 658 pages; 28 × 19.5 cm. December, 1944. Tip. do Gabinete de Investigações, Rua dos Gusmões, 300. São Paulo, Brasil.

Memoria de la Secretaria de Salubridad y Asistencia. 420 pages; 30 × 23.5 cm. 1943–1944. Secretaria de Salubridad y Asistencia, Mexico, D. F.

COLLEGE NEWS NOTES

. . . And Now the Future!

These News Notes are being gathered for the September number on V–J Day, and uppermost in the minds of all of us is the Future—our personal futures, the World future, the American future, the future of our institutions, the future, in particular, of the American College of Physicians.

During the War the College waived dues and fees of its members serving in the armed forces aggregating upward of $85,000.00, yet by careful management and inspired leadership it has successfully carried on and even increased many of its services. It has come through the war stronger than it entered. Classification of physicians for military duty, organization of the War-Time Graduate Medical Meetings for medical officers, conduct of regional meetings all over the United States so long as transportation facilities permitted, extension of the postgraduate course program are but a few of the activities of the College during the war. The journal, Annals of Internal Medicine, has been kept on a high plane, with little reduction in volume. The Executive Offices have functioned efficiently and effectively, with courtesy and service to all. There has been a steady though somewhat reduced growth in membership.

. . . And Now the Future. In June, 1945, the Board of Regents directed the further organization of its educational program under an educational director, working under the Regents and the Executive Secretary. It is hoped that by the time of publication of the September issue of this journal the educational director will have been appointed and ready to carry on. The program includes: (1) Reëstablishment of several Research Fellowships; (2) Resumption of annual award of the John Phillips Memorial Medal for research already accomplished; (3) Establishment of numerous Clinical Fellowships; (4) A marked extension of the postgraduate courses, especially to accommodate members returning from military service; (5) A service department to aid members retiring from military service to find residencies, assistantships and/or locations for work. The Executive Offices will welcome the suggestions and aid of its entire membership. A task worth doing must be well done.

Already the autumn program of postgraduate courses has been organized and announced. Just as soon as conditions permit, the great Annual Sessions and Regional Meetings of the College will be resumed—certainly the possibilities are promising for 1946.

"All for one and one for all," age worn though it may be, is an appropriate slogan as we work for the future.

A. C. P. Members in the Armed Forces

Previously reported in these columns have been the names of 1,864 members of the American College of Physicians commissioned in the armed forces during the war. Of the new members elected during June, 1945, and published in the July number, 56 are on military duty. These, added to the following newly reported admissions, bring the total to 1,923, 36% of the total members, Fellows and Associates, of the College.

Newly reported admissions:

Seymour Jerome Gray, Chicago, Ill. (Lieutenant, MC, USNR)
Myron David Miller, Columbus, Ohio (Surgeon, USPHS)
Walter C. Nalty, Fort Bayard, N. M. (Lieutenant Colonel, MC, AUS)
Edwin J. Rose, Washington, D. C. (Colonel, MC, AUS)

Retirements:

Michael Bevilacqua, Woodhaven, L. I., N. Y.
Pascal F. Lucchesi, Philadelphia, Pa.
James L. McCartney, Garden City, N. Y.
William J. Norfleet, Shreveport, La.
William D. Reid, Kezar Falls, Maine
Leonard G. Rowntree, Philadelphia, Pa.
Martin Van Buren Teem, Marietta, Ga.

Some of these admissions and discharges are of a considerably passed date, but have only now been reported to the College. Members are urged to notify the Executive Offices, 4200 Pine St., Philadelphia 4, Pa., promptly of admissions or discharges, giving dates and changes of address.

Changes of Address

Members and subscribers, especially those on military duty, frequently fail to receive the Annals of Internal Medicine owing to failure to register their changes of address. This situation has never been so acute as at present. The Medical Corps of the Army and Navy cannot, or do not, always furnish "directory service" for the forwarding of journals; often second class material is destroyed, and not returned to the publisher even though the mailing wrapper or envelope bears the inscription, "Forwarding and return postage guaranteed." Owing to paper restrictions, publishers cannot guarantee replacement of undelivered journals. Physicians should promptly inform their societies and the publishers of journals to which they subscribe of address changes.

Fund Given to the College for Its Post-War Educational Program

In the July issue of this journal the Post-war Educational Program of the American College of Physicians was announced. Under an Educational Director, the College proposes to expand very considerably its program of postgraduate courses, to reëstablish several research Fellowships, to award numerous clinical Fellowships, and to assist its members returning from military and naval service in locating residencies, fellowships, locations for practice, etc.

Dr. Willard O. Thompson, F.A.C.P., Chicago, Director of the American College of Physicians' course in internal medicine at Chicago institutions during October and November, 1944, has turned over a balance, from unexpended receipts, of $713.30 to be added to the College funds for the promotion of its Post-war Educational Program. The College itself has appropriated to date a total of $35,000 for this program. The College has the experience and the machinery to perform an effective and valuable service. The extent of that service may be limited only by the amount of funds available. It is hoped that additional funds will be contributed from other sources, including Foundations and the manufacturers of ethical drugs and other medical supplies. The College program proposes to be one of action and of service, not one of mere words.

Gifts to the College Library

The following gifts to the College library of publications by members are gratefully acknowledged:

Colonel Julien E. Benjamin, F.A.C.P., Fort Devens, Mass.—1 reprint.
Dr. Nathan Blumberg, F.A.C.P., Philadelphia, Pa.—1 reprint.
Dr. R. H. Felix, F.A.C.P., Washington, D.C.—1 reprint.

Dr. Arthur Grollman, F.A.C.P., Dallas, Tex.—19 reprints.
Captain Byron Jay Hoffman (Associate), U. S. Army overseas—1 reprint.
Dr. E. E. Kattwinkel, F.A.C.P., West Newton, Mass.—1 reprint.
Dr. Louis I. Kramer, F.A.C.P., Providence, R. I.—1 reprint.
Lieutenant Colonel Robert B. Radl, F.A.C.P., St. Paul, Minn.—1 reprint.
Dr. William S. Reveno, F.A.C.P., Detroit, Mich.—2 reprints.
Dr. George X. Schwemlein (Associate), Chicago, Ill.—2 reprints.
Lieutenant Commander Charles M. Thompson (Associate), U. S. Navy overseas —2 reprints.

Report from the Office of the Surgeon General, U. S. Army

Lieutenant Colonel Staige D. Blackford, (MC), F.A.C.P., of Charlottesville, Va., is now Chief of the Medical Service at Valley Forge General Hospital, Phoenixville, Pa. He succeeds Lieutenant Colonel Maurice A. Schnitker, (MC), F.A.C.P., of Toledo, O., who was given an overseas assignment. Colonel Blackford spent two and a half years overseas as Chief of the Medical Service of the 8th Evacuation Hospital in North Africa and Italy. He was awarded the Legion of Merit. Before entering the Army he was Associate Professor of Internal Medicine at the University of Virginia.

Major Edgar Stillwell Gordon, (MC), F.A.C.P., Madison, Wis., has been promoted to Lieutenant Colonel.

Major General George F. Lull, F.A.C.P., Deputy Surgeon General, gave the keynote address on the occasion of the 170th anniversary of the Army Medical Department on July 27, 1945. After pointing out that today's Medical Department, more than one-half million strong, is gearing itself to new high standards in the care of American sick and wounded at home and abroad, he added, "We are justifiably proud of our World War II record of returning nearly ninety-seven of every hundred of our disabled soldiers to duty." General Lull spoke from Valley Forge, the birthplace of the Medical Department, founded by the Continental Congress upon the request of General George Washington.

Colonel John B. Youmans, (MC), F.A.C.P., Director of the Nutrition Division, recently visited various types of prisoner of war camps in the Ninth Service Command and made observations on dietary needs in relation to kind and amount of work performed. The operation of messes using mainly noncritical and ration-point-free items was studied and the effect of such dietaries on performance and response of prisoners was observed.

Centers for corneal transplant operations on suitable cases have been established at Valley Forge General and Dibble General Hospitals. Suitable cases will be sent to these centers.

Baruch Committee on Physical Medicine

That the Baruch Committee on Physical Medicine, established in 1944 by Bernard M. Baruch with a gift of $1,190,000, is achieving wholly satisfactory results is made clear in its first annual report recently forwarded to the founder by Dr. Frank H. Krusen, F.A.C.P., Director of the Committee.

In creating the Committee, Mr. Baruch announced that its purpose would be to advance and encourage the knowledge and practice of physical medicine throughout the nation and the world with the special aim of bringing its benefits to disabled veterans of the war and of assisting in their rehabilitation and restoration to working health and usefulness.

The committee has defined physical medicine as follows: "Physical medicine is that branch of medical science which, in conjunction with or succeeding surgery and

hospitalization, undertakes the long course of restoration to working activity by the employment of heat, light, water, electricity, massage, manipulation, exercise and mechanical devices." It is said that the committee's activities have caused increasing general interest in the field of medicine it fosters and growing coöperation and comprehension of it on the part of the public at large.

The medical schools of ten universities and colleges, extending over the United States, are participating. There is also a fellowship fund of $100,000 for the encouragement of medical students at the various institutions who may plan to make physical medicine their specialty and to devote their professional careers to it. Five fellowships have already been granted. The grants to the different institutions have been as follows: College of Physicians and Surgeons of Columbia University, $400,000; New York University College of Medicine, $250,000; Medical College of Virginia, $250,000; Massachusetts Institute of Technology, $50,000; University of Minnesota, $40,000; University of Southern California, $30,000; Harvard University, $25,000; University of Iowa, $15,000; Washington University of St. Louis, $10,000; University of Illinois, $15,000; Marquette University, $5,000. Harvard University received an additional special grant of $30,000 with which to establish a three-year fellowship program. The grant to Massachusetts Institute of Technology was made especially for the establishment of a laboratory for the training of Baruch fellows and other competent doctors interested in the field of physical medicine and for research and development in electronics in relation to the field.

Approximately fifty scientific papers dealing with different phases of physical medicine have been prepared and distributed by committee members.

Army Medical Library Seeking Collection of Photographs of Prominent Men in American Medicine

The Army Medical Library desires to obtain the coöperation of prominent Fellows of the American College of Physicians in building up its collection of portraits of persons prominent in the field of medicine. As part of its program to expand this collection, it would appreciate receiving autographed photographs, preferably 8 × 10 inches in size, and unmounted, of each Fellow of the College. Photographs should be plainly marked on the back with date and name of the subject and should be sent to: The Director, Army Medical Library, 7th Street and Independence Avenue, S.W., Washington 25, D. C.

The collection now includes some 10,000 photographs and prints of well known figures of the past 400 years. It is intended that this collection shall be enlarged continuously by securing additional portraits of notable physicians of the past as well as those of contemporary worthies. Each photograph will be catalogued and carefully preserved and made available for reproduction when required.

Colonel William P. Holbrook, (MC), F.A.C.P., Chief of Professional Services, Office of the Air Surgeon, has been assigned to assist the subcommittee of the Military Affairs Committee to carry on its investigation of alleged overstaffing of medical personnel in the Army under Senate Resolution 134. Senator Sheridan Downey, (D), of California, stated that Colonel Holbrook had been directed to assemble for the committee all possible statistics and data dealing with the subject and to have these and necessary supporting witnesses and recommendations ready for presentation to the Military Affairs Committee upon the reassembling of Congress in the autumn.

Major Michael Bevilacqua, (MC), F.A.C.P., will revert to inactive status on October 2. He entered the Army on July 15, 1942, as a First Lieutenant; his first and only assignment was in the 10th Medical Laboratory; after training and two

tours of maneuvers, the unit went to Europe in February, 1944, and there was assigned to the First Army. It landed on Normandie Beachhead on D–11 and participated in the campaigns of Normandie, Northern France, Rhineland, Ardennes and Central Germany.

Major Bevilacqua was flown to the United States on July 14 and soon thereafter was notified of his release from active duty. He was awarded the Bronze Star Medal by General Hodges for meritorious service and his unit was awarded the Meritorious Service Unit Plaque for Superior Performance of Duty.

Colonel Henry Morgan Winans, (MC), F.A.C.P., at present Chief of the Medical Service, Brooke General Hospital, Fort Sam Houston, Texas, has recently received the honorary degree of Doctor of Laws from Baylor University.

Dr. Victor F. Cullen, F.A.C.P., State Sanatorium, Md., has been made President-elect of the National Tuberculosis Association. Dr. Cullen recently received the honorary degree of LL.D. from Mt. St. Mary's College, Emmitsburg, Md.

Dr. Joseph T. Roberts (Associate), Washington, D. C., made the following recent addresses: (1) "Experiments on the Rôle of the Small Blood Vessels in Heart Failure, Coronary Artery Disease and Heart Pain" before the Washington Heart Association; (2) "Barbiturate Poisoning" before the Doctors' Hospital staff; (3) "Picrotoxin and Other Aspects of Barbiturate Poisoning" before the staff of Anderson Clinic.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., Chairman of the Committee on Nutrition of the Medical Society of the State of Pennsylvania, addressed the Pennsylvania Chautauqua at Mount Gretna, Pennsylvania, on July 18, 1945, on "Food and Effects," followed by an illustrative film.

Lieutenant Colonel John W. Shuman, (MC), F.A.C.P., now attached to the Wadsworth General Hospital at West Los Angeles, California, has been awarded a silver plaque by the Hollywood Academy of Medicine for meritorious service as its President, 1937.

Colonel Shuman has been elected an honorary member of the American Geriatric Society.

Dr. Hobart A. Reimann, F.A.C.P., Professor of Medicine at Jefferson Medical College, recently flew to Chungking with six other members of a medical commission to aid in combating the cholera epidemic in the Chinese capital. The commission consists of five doctors and two sanitary engineers and was organized by the United Nations Relief and Rehabilitation Administration at the request of the Chinese Government and Lieutenant General A. C. Wedemeyer, commanding U. S. forces in the Chinese theater. The Chungking epidemic began in June. By the middle of July when Dr. Reimann left there were over 8,000 cases of cholera in the area of the Chinese capital.

Lieutenant Colonel Pascal F. Lucchesi, (MC), (Associate), has been released from active duty and will resume his former work as Superintendent and Medical Director of the Philadelphia Hospital for Contagious Diseases.

Dr. Harold Inman Gosline, F.A.C.P., formerly of Ossining, N. Y., is now Assistant Superintendent and Senior Psychiatrist to the New Mexico State Hospital at Las Vegas.

Dr. J. C. Geiger, F.A.C.P., Director of Public Health, City and County of San Francisco, is the recipient of the decoration of the Orden de Vasco-Nunez de Balboa of the Republic of Panama, "for distinguished, distinctive and generous services in public health given over a long period of time to the residents from Panama and to Panama, and a living example of the perpetuation and enrichment of Pan-Americanism." This decoration is named for Vasco-Nunez de Balboa, the noted Spanish traveler, discoverer and historian who pointed out to the world and posterity that the Isthmus of Panama was the life-line of the American continents.

Colonel Kemp Appointed Dean, Wayne University College of Medicine

Lt. Col. Hardy A. Kemp, (MC), Secretary of the Army Medical School, Washington, D. C., a graduate of St. Louis University School of Medicine, 1926, and formerly Dean of Ohio State University College of Medicine, Columbus, has been appointed Dean of the Wayne University College of Medicine, Detroit.

Dr. Harry J. Perlberg, F.A.C.P., Jersey City, has been elected President of the Radiological Society of New Jersey.

Ohio State University College of Medicine Announces Graduate Training for Veterans

Ohio State University College of Medicine recently announced a plan for postgraduate training, primarily for returning veterans and for interested physicians. Participants will be required to spend full time in the University Hospital or affiliated institutions of the Medical School for a period of not less than 2 weeks nor longer than 3 months, and will be under the direct supervision of a member of the faculty who will serve as a counselor.

For additional information, write Dr. Bruce K. Wiseman, F.A.C.P., Kinsman Hall, Ohio State University College of Medicine, Columbus 10, Ohio.

Dr. John O. Piper, F.A.C.P., of Waterville, Maine, has been chosen President-elect of the Maine Medical Association.

Dr. Francis G. Blake, F.A.C.P., and Regent, A.C.P., was presented with the Charles V. Chapin Memorial Award of the city of Providence for 1945. Dr. Blake is Dean and Sterling Professor of Medicine at Yale University. He delivered the annual Chapin Oration before the local medical society on "Some Recent Advances in the Control of Infectious Diseases."

Dr. Ralph A. Kinsella, F.A.C.P., St. Louis, has been appointed by Governor Donnelly to the Missouri State Board of Health for a 4-year term.

Dr. Clarence H. Beecher, F.A.C.P., will relinquish his Acting Deanship and in the future devote his full time to the Professorship of Medicine at the University of Vermont College of Medicine. Dr. William Eustis Brown, Associate Professor of Preventive Medicine at the University of Cincinnati College of Medicine, will be the full time Dean at the University of Vermont College of Medicine, effective September 1.

Dr. Myron D. Miller, F.A.C.P., formerly of Columbus, Ohio, has entered the U. S. Public Health Service as a regular and permanent officer as of July 16, 1945.

A.C.P. POSTGRADUATE COURSES

On the inside back cover page of this issue will be found the complete schedule and announcement of the Postgraduate Courses offered by the American College of Physicians. Numerous advance reservations have been coming in regularly and members are urged to complete registration as far in advance as possible.

The detailed outlines of the courses, faculty personnel, and other announcements will appear in the Postgraduate Bulletin which will be sent automatically to all members of the College. Non-members can obtain copies of the Bulletin by writing to the Executive Offices, 4200 Pine St., Philadelphia 4, Pa.

At the time this notice is being prepared for press, directors of some of the courses have not yet sent in their full outlines, and hence they cannot be published in this issue. However, such outlines as are available follow:

COURSE NO. 1—ALLERGY

(October 8–13, 1945)

Roosevelt Hospital, New York, N. Y.

ROBERT A. COOKE, M.D., F.A.C.P., *Director*

(Minimal Registration, 25; Maximal Registration, 50)

Officers of Instruction

Robert A. Cooke, M.D., F.A.C.P., Attending Physician and Director, Department of Allergy, Roosevelt Hospital.

Horace S. Baldwin, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Assistant Attending Physician and Chief of Allergy Clinic, New York Hospital.

Otelia J. Bengtsson, M.D., Clinical Assistant, Department of Allergy, Roosevelt Hospital.

Lilian A. Boker, M.D., Assistant Attending in Pediatrics and Clinical Assistant, Department of Allergy, Roosevelt Hospital.

Walter Brandes, M.D., Pathologist, Roosevelt Hospital.

Robert Chobot, M.D., F.A.C.P., Assistant Professor of Clinical Pediatrics, New York Post-Graduate Medical School and Hospital, Columbia University; Chief of Pediatric Allergy, New York Post-Graduate Medical School and Hospital; Assistant Chief, Allergy Clinic, Roosevelt Hospital.

Russell Clark Grove, M.D., Associate Surgeon, Otolaryngology, Roosevelt Hospital.

Joseph Harkavy, M.D., Associate in Medicine, Columbia University College of Physicians and Surgeons; Associate Physician and Chief of Allergy Clinic, Mt. Sinai Hospital; Associate Physician, Montefiore Hospital.

Selian Hebald, M.D., Assistant Chief of Allergy Clinic, Roosevelt Hospital; Senior Clinical Assistant in Allergy, Outpatient Department, Mt. Sinai Hospital.

Foster Kennedy, M.D., Professor of Neurology, Cornell University Medical College; Director, Neurological Department, Bellevue Hospital.

Paul Klemperer, M.D., Pathologist, Mt. Sinai Hospital.

Louis Schwartz, M.D., Medical Director, Chief, Dermatoses Section, U. S. Public Health Service, Bureau of State Services, Bethesda, Md.

Will Cook Spain, M.D., F.A.C.P., Clinical Professor of Medicine, New York Post-Graduate School and Hospital, Columbia University; Chief of Allergy Clinic and Attending Physician, New York Post-Graduate Medical School and Hospital.

Albert Vander Veer, M.D., Consultant in Allergy and Chief of Allergy Clinic, Roosevelt Hospital.

Matthew Walzer, M.D., Associate in Medicine, Cornell University Medical College; Attending in Allergy and Chief of Allergy Clinic, Jewish Hospital, Brooklyn.

Although the course in Allergy will be given at the Roosevelt Hospital, the faculty consists of members of various medical schools and hospitals in New York and the U. S. Public Health Service. All important phases of allergy will be covered in lectures and clinics on the theoretical and practical aspects of the subject.

This year a special feature is made of colloquia on Friday afternoon and Saturday morning. In this way small groups will be given an opportunity for free and informal discussion with various faculty members of assigned topics, and any subject not adequately covered in formal lectures may be brought up for consideration. It is requested that registrants indicate their first, second and third choices, and assignments will be made as closely as possible with the expressed choices of the registrants.

A reference list of desirable articles on allergy will be mailed to all registrants from the office of the American College of Physicians.

Outline of Course

Monday, October 8.

A.M. Session

9:00–11:30 Registration.
Fundamentals of Allergy and Allergic Disease.
Dr. Cooke.

11:30– 1:00 Allergen Extracts: Preparation and Standardization.
Dr. Spain.

P.M. Session

2:00– 4:00 Skin Testing: Methods and Interpretations.
Dr. Walzer.

4:00– 6:00 Pathologic Anatomic Aspects of Allergic Disease.
Dr. Klemperer.

Tuesday, October 9.

Asthma

A.M. Session

9:00–11:00 Infective Asthma.
Dr. Cooke.

11:00– 1:00 Non-Infective Asthma.
Dr. Spain.

P.M. Session

2:00– 4:00 Differential Diagnosis and Treatment of Status Asthmaticus.
Dr. Baldwin.

4:00– 6:00 Pathology of Asthma.
Dr. Brandes.

Wednesday, October 10.

Allergic Rhinitis

A.M. Session

9:00–11:00 Seasonal Type (1st session).
Dr. Vander Veer.

11:00– 1:00 Perennial Type.
Dr. Spain.

P.M. Session

2:00– 3:30 Seasonal Type (2nd session).
Dr. Vander Veer.

3:30– 4:30 Seasonal Hay Fever: Special Problems.
Dr. Hebald.

4:30– 6:00 Sinus Infection and Allergic Disease.
Dr. Grove.

Thursday, October 11.

A.M. Session

9:00–10:00 Mold Allergy.
Dr. Chobot.

10:00–11:00 Pediatric Allergy.
Dr. Chobot.

11:00– 1:00 Industrial Dermatoses (Contact Dermatosis).
Dr. Schwartz.

P.M. Session

2:00– 4:00 Eczema: Diagnosis; Specific and Symptomatic Therapy.
Dr. Cooke.

4:00– 6:00 Clinic.
Dr. Cooke.

Friday, October 12.

A.M. Session

9:00–11:00 Vascular Allergy; Meniere's Disease; Migraine.
Dr. Harkavy.

11:00– 1:00 Urticaria, Angioneurotic Edema and Gastrointestinal Allergy.
Dr. Cooke.

P.M. Session

2:00– 4:00 Allergy and the Central Nervous System.
Dr. Kennedy.

4:00– 6:00 Colloquia:

I. Skin Testing: Gastrointestinal Allergy, Physical Allergy.
Dr. Walzer.

II. Vascular Allergies: Migraine; Meniere's Disease.
Dr. Harkavy.

III. Asthma: Allergic Rhinitis; Perennial.
Dr. Spain.

IV. Allergic Rhinitis: Seasonal; Mold Allergy.
Dr. Vander Veer.

V. Allergic Dermatoses.
Dr. Cooke.

Saturday, October 13.

A.M. Session

9:00–12:00 Colloquia:

I. Allergy Clinic.
Allergy Clinic Set-up.
Care of Syringes and Extracts.
Practice in Skin Testing.
Preparation of Extracts—Standardization.
Care of Pollen.
Passive Transfer Tests.
Modification of Extracts.
Drs. Hebald, Boker and Bengtsson.

9:00–10:30

II. Rhinological Examination and Diagnosis.
Dr. Grove.

III. Pediatric Allergy—Mold Allergy.
Dr. Chobot.

IV. Principles of Allergy. Asthma.
Dr. Cooke.

V. Allergic Rhinitis.
Dr. Vander Veer.

10:30–12:00 VI. Food Allergy: Urticaria; Angio Edema.
Dr. Chobot.
VII. Vernal Catarrh: Histamine—Hapamine.
Dr. Cooke.
VIII. Drug and Serum Allergy.
Dr. Harkávy.

COURSE NO. 2—INTERNAL MEDICINE

(October 15–27, 1945)

University of Michigan Medical School and University Hospital
Ann Arbor, Michigan

CYRUS C. STURGIS, M.D., F.A.C.P., *Director*

(Minimal Registration, 20; Maximal Registration, 50)

Fees: A.C.P. Members, $40.00; Non-members, $80.00; Military Officers (active), Free

Officers of Instruction

John Alexander, M.A., Sc.D., M.D., F.A.C.S., Professor of Surgery.
Carl E. Badgley, M.D., F.A.C.S., Professor of Surgery.
Carl D. Camp, M.D., Professor of Neurology and Chairman of the Department.
Frederick A. Coller, M.S., M.D., F.A.C.S., Professor of Surgery and Chairman of the Department.
Arthur C. Curtis, M.D., F.A.C.P., Professor of Dermatology.
Albert C. Furstenberg, M.D., F.A.C.S., Professor of Otology, Chairman of the Department and Dean of the Medical School.
Fred J. Hodges, M.D., Professor of Roentgenology and Chairman of the Department.
Norman F. Miller, M.D., F.A.C.S., Professor of Obstetrics and Gynecology and Chairman of the Department.
Reed M. Nesbit, M.D., F.A.C.S., Professor of Surgery.
Louis H. Newburgh, M.D., F.A.C.P., Professor of Internal Medicine.
Max M. Peet, M.D., F.A.C.S., Professor of Surgery.
Maurice H. Seevers, M.D., Professor of Pharmacology and Chairman of the Department.
Cyrus C. Sturgis, M.D., F.A.C.P., Professor of Internal Medicine and Chairman of the Department.
Raymond W. Waggoner, M.D., Professor of Psychiatry and Chairman of the Department.
Carl V. Weller, M.D., F.A.C.P., Professor of Pathology and Chairman of the Department.
Frank N. Wilson, M.D., F.A.C.P., Professor of Internal Medicine.
Paul S. Barker, M.D., Associate Professor of Internal Medicine.
John B. Barnwell, M.D., Associate Professor of Internal Medicine.
Frank H. Bethell, M.D., F.A.C.P., Associate Professor of Internal Medicine and Assistant Director of Simpson Memorial Institute.
Jerome Conn, M.D., F.A.C.P., Associate Professor of Medicine.
Franklin D. Johnston, M.D., Associate Professor of Internal Medicine and Secretary of the Medical School.
Richard H. Lyons, M.D., F.A.C.P., Associate Professor of Internal Medicine.

H. Marvin Pollard, M.D., F.A.C.P., Associate Professor of Internal Medicine.
John D. Adcock, M.D., F.A.C.P., Assistant Professor of Internal Medicine.
William D. Robinson, M.D., F.A.C.P., Assistant Professor of Internal Medicine, in charge of Rackham Arthritis Research.
Francis F. Rosenbaum, M.D., Assistant Professor of Internal Medicine.
Robert A. Hettig, M.D., Instructor in Internal Medicine.
Daniel E. Jenkins, M.D., Instructor in Internal Medicine.

This program is designed to give a survey of the recent developments in medicine. It consists of clinics, ward demonstrations and conferences, with ample opportunity for discussion of the subjects presented.

Outline of Course

Monday, October 15.

A.M. Session

8:00– 9:00 Registration. Room 2040, University Hospital.
9:00–11:00 Ward Rounds.
Thyroid Diseases. Section A: 2NE.
Dr. Sturgis.
Diabetes. Section B: 2NW
Dr. Conn.
11:00–12:00 Post-war Nutrition Problems.
Dr. Robinson.
12:00–12:40 Motion Picture of Selected Medical Topics.

P.M. Session

1:30– 2:30 Abuse of Rest in Surgery.
Dr. Coller.
2:30– 3:30 Demonstrations.
Section A: Blood Transfusions.
Section B: Arthritis Unit.
3:30– 5:00 Clinical Pharmacological Conference.
Dr. Sturgis, Dr. Seevers and the Medical Staff.
8:00 Smoker, Washtenaw Country Club.

Tuesday, October 16.

A.M. Session

9:00–11:00 Ward Rounds.
Diabetes. Section A.
Dr. Conn.
Thyroid Diseases. Section B.
Dr. Sturgis.
11:00–12:00 Electrocardiographic Changes in Myocardial Infarction.
Dr. Wilson.
12:00–12:40 Motion Picture of Selected Medical Topics.

P.M. Session

1:30– 2:30 Surgical Treatment of Hypertension.
Dr. Peet.
2:30– 3:30 Demonstrations.
Section A: Arthritis Unit.
Section B: Blood Transfusions.
3:30– 5:00 Electrocardiographic Conference.
Dr. Wilson and the Medical Staff.

Wednesday, October 17.

A.M. Session

9:00–11:00 Ward Rounds.
Cardiac Failure. Section A.
Dr. Lyons.
Hypertension. Section B.
Dr. Barker.

11:00–12:00 Paroxysmal Rapid Heart Action.
Dr. Rosenbaum.

12:00–12:40 Motion Picture of Selected Medical Topics.

P.M. Session

1:30– 2:30 Intrathoracic Tumors.
Dr. Alexander.

2:30– 3:30 Demonstrations.
Section A: Heart Station.
Section B: Tropical Medicine.

3:30– 5:00 X-Ray Medical Conference.
Dr. Hodges, Dr. Sturgis and the Medical Staff.

Thursday, October 18.

A.M. Session

9:00–11:00 Ward Rounds.
Hypertension. Section A.
Dr. Barker.
Cardiac Failure. Section B.
Dr. Lyons.

11:00–12:00 Kidney Function.
Dr. Newburgh.

12:00–12:40 Motion Picture of Selected Medical Topics.

P.M. Session

1:30– 2:30 Tuberculosis of the Urinary Tract.
Dr. Nesbit.

2:30– 3:30 Demonstrations.
Section A: Tropical Medicine.
Section B: Heart Station.

3:30– 5:00 Medical Staff Conference.
Dr. Sturgis and the Medical Staff.

Friday, October 19.

A.M Session

9:00–11:00 Ward Rounds.
Nephritis. Section A.
Dr. Newburgh.
Allergy. Section B.
Dr. Jenkins.

11:00–12:00 Spontaneous Hypoglycemia.
Dr. Conn.

12:00–12:40 Motion Picture of Selected Medical Topics.

P.M. Session

1:30– 2:30 The Problem of the Positive Serological Test for Syphilis.
Dr. Curtis.

2:30– 3:30 Demonstrations.
Section A: Allergy Clinic.
Section B: Gastroscopy.

3:30– 5:00 Clinical Pathological Conference.
Dr. Weller and the Medical Staff.

Saturday, October 20.

A.M. Session

9:00–11:00 Ward Rounds.
Allergy. Section A.
Dr. Jenkins.
Nephritis. Section B.
Dr. Newburgh.

11:00–12:00 Disturbances of Leukopoiesis.
Dr. Bethell.

Monday, October 22.

A.M. Session

9:00–11:00 Ward Rounds.
Peptic Ulcer. Section A.
Dr. Pollard.
Subacute Bacterial Endocarditis. Section B.
Dr. Barker.

11:00–12:00 Some Disturbances in the Dynamics of the Circulation.
Dr. Lyons.

12:00–12:40 Motion Picture of Selected Medical Topics.

P.M. Session

1:30– 2:30 Sinusitis.
Dr. Furstenberg.

2:30– 3:30 Demonstrations.
Section A: Simpson Institute.
Section B: Neuropsychiatric Institute.

3:30– 5:00 Surgical-Medical Conference.
Dr. Coller, Dr. Sturgis and the Medical and Surgical Staffs.

Tuesday, October 23.

A.M. Session

9:00–11:00 Ward Rounds.
Subacute Bacterial Endocarditis. Section A.
Dr. Barker.
Peptic Ulcer. Section B.
Dr. Pollard.

11:00–12:00 Tuberculosis, the Minimal Lesion.
Dr. Barnwell.

12:00–12:40 Motion Picture of Selected Medical Topics.

P.M. Session

1:30– 2:30 The Dysenteries.
Dr. Pollard.

2:30– 3:30 Demonstrations.
Section A: Neuropsychiatric Institute.
Section B: Simpson Institute.

3:30– 5:00 Obstetrical-Medical Conference.
Dr. Miller, Dr. Sturgis and the Medical and Obstetrical Staffs.

Wednesday, October 24.

A.M. Session

9:00–11:00 Ward Rounds.
Coronary Artery Disease. Section A.
Dr. Johnston.
Liver Disease. Section B.
Dr. Pollard.

11:00–12:00 Antibiotics.
Dr. Adcock.
12:00–12:40 Motion Picture of Selected Medical Topics.
P.M. Session
1:30– 2:30 Pain of Spinal Origin.
Dr. Badgley.
2:30– 3:30 Demonstrations.
Section A: Diet Therapy.
Section B: TB Unit.
3:30– 5:00 X-Ray Medical Conference.
Dr. Hodges, Dr. Sturgis and the Medical Staff.

Thursday, October 25.

A.M. Session
9:00–11:00 Ward Rounds.
Biliary and Liver Disease. Section A.
Dr. Pollard.
Coronary Artery Disease. Section B.
Dr. Johnston.
11:00–12:00 Treatment of Anemia.
Dr. Sturgis.
12:00–12:40 Motion Picture of Selected Medical Topics.
P.M Session
1:30– 2:30 Senescence.
Dr. Camp.
2:30– 3:30 Demonstrations.
Section A: TB Unit.
Section B: Diet Therapy.
3:30– 5:00 Medical Staff Conference.
Dr. Sturgis and the Medical Staff.

Friday, October 26.

A.M. Session
9:00–11:00 Ward Rounds.
Obesity. Section A.
Dr. Newburgh.
Endocrinology. Section B.
Dr. Conn.
11:00–12:00 Gastritis.
Dr. Pollard.
12:00–12:40 Motion Picture of Selected Medical Topics.
P.M. Session
1:30– 2:30 Modern Treatment of Syphilis.
Dr. Curtis.
2:30– 3:30 Demonstrations.
Section A: Gastroscopy.
Section B: Allergy Clinic.
3:30– 5:00 Clinical Pathological Conference.
Dr. Weller and the Medical Staff.

Saturday, October 27.

A.M. Session
9:00–11:00 Ward Rounds.
Endocrinology. Section A.
Dr. Conn.

Obesity. Section B.
Dr. Newburgh.
11:00–12:00 Question Period.
Dr. Sturgis and the Medical Staff. Room 2330.

COURSE NO. 3—GENERAL MEDICINE

(October 29—November 3, 1945)

University of Oregon Medical School, Portland, Ore.

HOMER P. RUSH, M.D., F.A.C.P., *Director*

(Maximal Registration, 25)

Officers of Instruction

Guests

Major Ercell A. Addington, MC, Barnes General Hospital, Vancouver, Wash.
Colonel Charles K. Berle, MC, F.A.C.P., Barnes General Hospital, Vancouver, Wash.
Lieutenant Colonel Orlando B. Mayer, MC, F.A.C.P., Barnes General Hospital, Vancouver, Wash.
Major Walter R. Nickel, MC, Barnes General Hospital, Vancouver, Wash.
Major William W. Waddell, MC, Barnes General Hospital, Vancouver, Wash.
Colonel Irving S. Wright, MC, F.A.C.P., Medical Consultant, Ninth Service Command, Fort Douglas, Utah.

University of Oregon Medical School Faculty

David W. E. Baird, M.D., F.A.C.P., Dean, Professor of Medicine.
John H. Benward, M.D., Assistant Professor of Pediatrics.
Joseph B. Bilderback, M.D., Professor of Pediatrics, Head of Dept.
T. Homer Coffen, M.D., F.A.C.P., Clinical Professor of Medicine.
Rudolph M. Crommelin, M.D., Clinical Instructor in Medicine.
Joyle O. Dahl, M.D., Assistant Clinical Professor of Dermatology.
Norman A. David, M.D., Professor; Head of Dept. of Pharmacology and Clinical Instructor in Medicine.
Wesley E. Gatewood, M.D., Assistant Clinical Professor of Medicine.
Leon A. Goldsmith, M.D., F.A.C.P., Assistant Clinical Professor of Medicine.
Morton J. Goodman, M.D., Assistant Clinical Professor of Medicine.
Hance F. Haney, M.D., Professor of Physiology.
Carl Heller, M.D., Clinical Instructor in Medicine.
Blair Holcomb, M.D., F.A.C.P., Assistant Clinical Professor of Medicine.
Charles N. Holman, M.D., Medical Director of Hospitals.
John J. Krygier, M.D., Instructor in Medicine.
John H. Labadie, M.D., Assistant Clinical Professor of Dermatology and Syphilology.
Donald R. Laird, M.D., Assistant Clinical Professor of Surgery.
Guy R. McCutchan, M.D., F.A.C.P., Clinical Instructor in Medicine.
Frank R. Mount, M.D., F.A.C.P., Assistant Clinical Professor of Medicine.
Lawrence Noall, M.D., Associate Professor of Orthopedic Surgery.
Edwin E. Osgood, M.D., F.A.C.P., Associate Professor of Medicine; Head of the Division of Experimental Medicine.
John Pierson, M.D., Resident in Medicine.
Matthew C. Riddle, M.D., Associate Professor of Medicine.
Homer P. Rush, M.D., F.A.C.P., Associate Professor of Medicine.

Laurence Selling, M.D., F.A.C.P., Professor of Neurology; Head of the Division.
James T. Speros, M.D., Assistant Professor of Medicine.
Marvin Schwartz, M.D., Clinical Instructor in Medicine.
Ben Vidgoff, M.D., Clinical Instructor in Medicine.
Charles P. Wilson, M.D., Assistant Clinical Professor of Medicine.

The purpose of this course is to review specific phases of medicine as it pertains to the Internist. This course will be given by members of the faculty with the help of members from the staff at Barnes General Hospital, and Colonel Irving S. Wright, Medical Consultant of the Ninth Service Command.

The program will be arranged to include lectures and informal discussions, round table meetings, and clinical conferences. It is hoped the class will take part in the latter both with questions and discussions.

The headquarters hotel will be the Heathman. All meetings will be held at the Medical School except for the round table discussions which will be held at the Heathman Hotel and the Tuesday afternoon meeting which will be given at Barnes General Hospital, Vancouver, Washington. It is hoped that those planning to come will make early hotel reservations. The program this year has been arranged to allow more time at noon, adequate time for transportation and shorter periods than last year's course.

Outline of Course

Monday, October 29.

A.M. Session—Medical School, Library
Chairman: Dr. Rush.

8:00– 9:00 Registration and Welcome.
Drs. Baird, Selling and Rush.
9:00– 9:40 Psychosomatic Medicine.
Dr. Selling.
9:40–10:20 Interpretation of Chest Signs.
Dr. Osgood.
10:20–10:30 Intermission.
10:30–11:00 Anemias.
Dr. Riddle.
11:00–11:40 The Adrenal.
Dr. Rush.
11:40–12:30 Transportation Time.

Heathman Hotel

12:30– 1:50 Round Table Discussion—Treatment of Syphilis
Drs. Dahl, Goodman and Labadie.
1:50– 2:10 Transportation Time.

P.M. Session—Medical School
Chairman: Dr. Coffen.

2:10– 3:30 Clinical Conference.
Dr. Mount.
3:30– 3:40 Intermission.
3:40– 4:20 Myth of the Enlarged Heart.
Dr. Coffen.
4:20– 5:00 Rectal Diseases.
Dr. Laird.

Tuesday, October 30.

A.M. Session—Medical School, Library
Chairman: Dr. Selling.

9:00– 9:40 Psychosomatic Medicine.
Dr. Selling.
9:40–10:20 Hepatitis.*
Colonel Wright.
10:20–10:30 Intermission.
10:30–11:00 Anemias.
Dr. Riddle.
11:00–11:40 The Adrenal.
Dr. Heller.
11:40 Transportation Time.

Afternoon Session at Barnes General Hospital arranged by Colonel Berle, Commanding. Starting at 1:30 at the Red Cross Lecture Hall. The following program is subject to change depending upon Army personnel.
Chairman: Colonel Berle.

1:30– 2:15 Lesions of the Oral Cavity as an Aid to Diagnosis.
Major Nickel.
2:15– 3:00 Clinical Observation in Intestinal Infections.
Major Waddell.
3:00– 3:45 Massive Doses of Penicillin in the Treatment of Bacterial Endocarditis.
Lieutenant Colonel Mayer.
3:45 Roentgenologist and Antral Gastritis.
Major Addington.
5:00 Tour of Hospital.

Wednesday, October 31.

A.M. Session—Medical School, Library
Chairman: Dr. Riddle.
9:00– 9:40 Headaches.
Dr. Selling.
9:40–10:20 Peripheral Vascular Disease.*
Colonel Wright.
10:20–10:30 Intermission.
10:30–11:00 White Blood Cell Diseases.
Dr. Riddle.
11:00–11:40 The Adrenal.
Dr. Heller.
11:40–12:30 Transportation Time.

Heathman Hotel

12:30– 1:50 Round Table Discussion—Rheumatic Fever.
Drs. Rush, Wright, Bilderback and Osgood.
1:50– 2:10 Transportation Time.

P.M. Session—Medical School, Library
Chairman: Dr. Goldsmith.
2:10– 3:30 Clinical Conference.
Dr. Selling.
3:30– 3:40 Intermission.
3:40– 4:20 Classification of Tuberculosis.
Dr. Speros.
4:20– 5:00 Medical Bone Diseases.
Dr. Noall.

* Informal discussion with questions.

Thursday, November 1.

A.M. Session—Medical School, Library

Chairman: Dr. Holman.

9:00– 9:40 Heart Tones.
Dr. Goodman.

9:40–10:20 Unipolar Leads.
Dr. Schwartz.

10:20–10:30 Intermission.

10:30–11:00 White Blood Cell Diseases.
Dr. Riddle.

11:00–11:40 The Adrenal.
Dr. Heller.

11:40–12:30 Transportation Time.

Heathman Hotel

12:30– 1:50 Round Table Discussion—Obesity.
Drs. Rush, Vidgoff, Heller and Crommelin.

1:50– 2:10 Transportation Time.

P.M. Session—Medical School

Chairman: Dr. Osgood.

2:10– 3:30 Clinical Conference.
Dr. Osgood.

3:30– 3:40 Intermission.

3:40– 4:20 Classification of Tuberculosis.
Dr. Speros.

4:20– 5:00 Medical Bone Diseases.
Dr. Noall.

Friday, November 2.

A.M. Session—Medical School, Library

Chairman: Dr. Goodman.

9:00– 9:40 Heart Tones.
Dr. Goodman.

9:40–10:20 Unipolar Leads.
Dr. Schwartz.

10:20–10:30 Intermission.

10:30–11:00 Hemorrhagic Diseases.
Dr. Riddle.

11:00–11:40 The Adrenal.
Dr. Heller.

11:40–12:30 Transportation Time.

Heathman Hotel

12:30– 1:50 Round Table Discussion—Antibiotics.
Drs. Osgood, David and Benward.

1:50– 2:10 Transportation Time.

P.M. Session—Medical School

Chairman: Dr. McCutchan.

2:10– 3:30 Clinical Conference.
Dr. Gatewood.

3:30– 3:40 Intermission.

3:40– 4:20 Cor Pulmonale.
Dr. Krygier.

4:20– 5:00 Medical Bone Diseases.
Dr. Noall.

Saturday, November 3.

A.M. Session—Medical School, Library

Chairman: Dr. Mount.

9:00– 9:40 The Clinical Approach in the Care of the Chronic Patient.
Dr. Holcomb.

9:40–10:20 Acid Ash Diet.*
Dr. Wilson.

10:20–10:30 Intermission.

10:30–11:00 Coronary Disease.
Dr. Mount.

11:00–11:40 Diabetes Insipidus.
Dr. Vidgoff.

11:40 Some Observations on the Carotid Sinus Reflex.
Drs. Haney and Pierson.

COURSE NO. 4—RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE

(November 5–10, 1945)

Massachusetts General Hospital, Boston, Mass.

PAUL D. WHITE, M.D., F.A.C.P., *Director*

(Minimal Registration, 30; Maximal Registration, 75)

Fees: A.C.P. Members, $20.00; Non-members, $40.00; Military Officers (active), Free

Officers of Instruction

Donald G. Anderson, M.D., Research Fellow in Medicine, Evans Memorial, Massachusetts Memorial Hospitals; Instructor in Medicine, Boston University School of Medicine.

William B. Bridges, M.D., Commonwealth Research Fellow, Massachusetts General Hospital.

C. Sidney Burwell, M.D., F.A.C.P., Physician, Peter Bent Brigham Hospital; Research Professor of Clinical Medicine and Dean, Harvard Medical School.

Mandel E. Cohen, M.D., Junior Visiting Neurologist, Boston City Hospital; Instructor in Neurology, Harvard Medical School.

Lewis Dexter, M.D., Associate in Medicine, Peter Bent Brigham Hospital; Associate in Medicine, Harvard Medical School.

Robert E. Gross, M.D., F.A.C.S., Associate Visiting Surgeon, Children's Hospital; Associate in Surgery, Peter Bent Brigham Hospital; Associate Professor of Surgery, Harvard Medical School.

Burton E. Hamilton, M.D., F.A.C.P., Consultant in Cardiology, Boston City Hospital and Boston Lying-In Hospital; Instructor in Medicine, Courses for Graduates, Harvard Medical School.

T. Duckett Jones, M.D., Research Director, House of the Good Samaritan; Assistant Physician, Massachusetts General Hospital; Associate Professor of Medicine, Harvard Medical School.

Samuel A. Levine, M.D., F.A.C.P., Physician, Peter Bent Brigham Hospital; Assistant Professor of Medicine, Harvard Medical School.

Robert R. Linton, M.D., F.A.C.S., Associate Visiting Surgeon, Massachusetts General Hospital; Instructor in Surgery, Harvard Medical School.

* Informal discussion with questions.

Benedict Massell, M.D., Research Associate, House of the Good Samaritan; Assistant in Medicine, Massachusetts General Hospital; Assistant in Medicine, Harvard Medical School.

Maurice B. Rappaport, E. E., Chief Engineer, Electrophysiologic Research, Sanborn Company.

Reginald H. Smithwick, M.D., F.A.C.S., Associate Visiting Surgeon, Massachusetts General Hospital; Instructor in Surgery, Courses for Graduates, Harvard Medical School.

Merrill C. Sosman, M.D., Radiologist, Peter Bent Brigham Hospital; Clinical Professor of Radiology, Harvard Medical School.

Howard B. Sprague, M.D., F.A.C.P., Associate Physician, Massachusetts General Hospital; Visiting Physician, House of the Good Samaritan; Instructor in Medicine, Courses for Graduates, Harvard Medical School.

Richard H. Sweet, M.D., F.A.C.S., Associate Visiting Surgeon, Massachusetts General Hospital; Instructor in Surgery, Harvard Medical School.

Helen B. Taussig, M.D., Pediatrician, Johns Hopkins Hospital; Associate in Pediatrics, Johns Hopkins University School of Medicine.

Edwin O. Wheeler, M.D., Graduate Assistant, Massachusetts General Hospital.

Paul D. White, M.D., F.A.C.P., Physician, Massachusetts General Hospital; Lecturer in Medicine, Harvard Medical School.

Conger Williams, M.D., Assistant in Medicine, Massachusetts General Hospital; Assistant in Medicine, Harvard Medical School.

This course is designed to give in one week a summary of the recent advances and present status of our knowledge of cardiovascular disease with particular emphasis on clinical aspects. With some omissions of inadequate summaries of anatomy, physiology, pharmacology, etc., and with more emphasis on clinical advances, and with a faculty selected with great care, this course will be essentially a repetition of the course organized by Dr. White for the College during the autumn of 1944.

It is regretted that no additional registrations can now be accepted for this course because its capacity has already been exceeded from advance applications from members of the College whose registrations emanated from announcements previously appearing in the Annals of Internal Medicine.

Outline of Course

Monday, November 5.

A.M. Session—Out-Patient Lower Amphitheatre.

9:00–10:00 Introductory remarks.
Important clues in cardiovascular symptoms and signs, with particular emphasis on newer observations.
Dr. White.

10:00–12:00 Auscultation with demonstration of phonocardiography and audible registration of heart sounds and murmurs.
Dr. Sprague and Mr. Rappaport.

12:00– 1:00 Advances in cardiovascular roentgenology.
Dr. Sosman.

P.M. Session—Ether Dome.

2:00– 3:00 Electrocardiography. Its historical development and present place in clinical medicine.
Dr. White.

3:00– 4:00 Recent advances in electrocardiography with particular reference to precordial leads.
Dr. Williams.

4:00– 5:00 Blood flow, circulation time, ballistocardiography.
Dr. Cohen.
Evening Session—Ether Dome.
8:00–10:00 Test electrocardiograms.
Dr. White.

Tuesday, November 6.

A.M. Session—Ether Dome.
9:00– 1:00 Present status and recent advances in diagnosis and treatment of congenital heart disease: Clinic.
Drs. Gross, Taussig and White.
P.M. Session—Ether Dome.
2:00– 3:30 Subacute bacterial endocarditis: Clinic. Present status and recent advances.
Drs. Anderson and Wheeler.
3:30– 5:00 Neurocirculatory asthenia: Clinic. Present status and recent advances.
Dr. Cohen.
Evening Session—Ether Dome.
8:00–10:00 Test x-rays.
Dr. White.

Wednesday, November 7.

A.M. Session—Ether Dome.
9:00– 1:00 Rheumatic fever and rheumatic heart disease: Clinic. Recent advances in diagnosis and treatment.
Drs. Jones and Massell.
Afternoon and evening free.

Thursday, November 8.

A.M. Session—Out-Patient Lower Amphitheatre.
9:00– 1:00 Hypertension and hypertensive heart disease: Clinic. Recent advances in diagnosis and treatment.
Drs. Dexter, Bridges, Smithwick and White.
P.M. Session—Ether Dome.
2:00– 5:00 Coronary heart disease: Clinic. Recent advances in diagnosis and treatment.
Dr. White and associates.
Evening Session—Ether Dome.
8:00–10:00 Test exercise in pathology.
Dr. White.

Friday, November 9.

A.M. Session—Ether Dome.
9:00– 1:00 Congestive heart failure: Clinic. Present status and recent advances.
Drs. White, Williams and Bridges.
P.M. Session—Ether Dome.
2:00– 5:00 The Arrhythmias.
Dr. White and associates.
Evening Session—Harvard Club.
8:00–10:30 Round Table Conference.
Drs. Burwell, Hamilton, Levine and White.

Saturday, November 10.

A.M. Session—Ether Dome.

9:00–11:00 Peripheral vascular disease: Clinic. Recent advances in diagnosis and treatment.
Dr. Linton.

11:00–12:00 Pericarditis: Clinic. Recent advances in diagnosis and treatment.
Drs. Sweet and White.

12:00– 1:00 The Cor Pulmonale.
Dr. White.
Concluding Remarks.

COURSE NO. 5—ENDOCRINOLOGY

(November 5–10, 1945)

Chicago and Other Institutions

Hotel Continental

505 North Michigan Avenue

Chicago, Illinois

WILLARD O. THOMPSON, M.D., F.A.C.P., *Director*

(Minimal Registration, 50; Maximal Registration, 100)

Fees: A.C.P. Members, $20.00; Non-members, $40.00; Military Officers (active), Free

This course offers an opportunity for physicians to bring themselves up to date in the field of endocrinology. The faculty of fifty-two includes many of the most outstanding endocrinologists from all over the United States and Canada. Numerous institutions are represented, including:

American College of Surgeons
American Medical Association
The Chicago Medical Society
Cleveland Clinic
Colorado State College
Columbia University
Cornell University Medical College
Duke University School of Medicine
Harvard Medical School
Johns Hopkins University
Marquette University School of Medicine
Mayo Foundation, University of Minnesota
The Medical Corps of the United States Army
Northwestern University Medical School
State University of Iowa College of Medicine
Tufts College Medical School
University of Chicago, The School of Medicine
University of Illinois College of Medicine
University of Oklahoma School of Medicine
University of Southern California
University of Toronto Faculty of Medicine

University of Utah School of Medicine
University of Wisconsin Medical School
Washington University School of Medicine

The physical arrangements for the course this year are ideal. The meetings will be held in the same hotel in which the men are living. An adequate number of guest rooms has been set aside and every effort will be made to contribute to the comfort of visiting physicians.

Meeting Place: Hotel Continental, 505 North Michigan Avenue—this is within walking distance of the Loop. All meetings will be held in the Boulevard Room, fifth floor, except those on Saturday, November 10, which will be held in the Tally-Ho Room on the ninth floor. This day will be devoted to the regional meeting of the American College of Physicians for the states of Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota and Wisconsin. This meeting is part of the Course and all physicians taking the Course whether they are members of the College or not are invited not only to participate in the scientific sessions of the regional meeting but also to attend the luncheon and the dinner.

Luncheon: Tally-Ho Room, ninth floor, Hotel Continental, November 5, 6, 7, 8 and 9. Boulevard Room, fifth floor, November 10.

Refreshments during intermissions: Gothic Room, third floor, Hotel Continental, November 5, 6 and 7; Tropical Room, fifth floor, November 8 and 9.

Officers of Instruction

Raymond B. Allen, M.D., F.A.C.P., Dean, University of Illinois College of Medicine.
William Allen, M.D., Professor of Gynecology and Obstetrics, Washington University School of Medicine, St. Louis.
Alexander Brunschwig, M.D., F.A.C.S., Professor of Surgery, University of Chicago, The School of Medicine.
Eben Carey, M.D., Professor of Anatomy and Dean, Marquette University School of Medicine.
Anton J. Carlson, LL.D., Ph.D., M.D., F.A.C.P., Professor of Physiology Emeritus, University of Chicago, The School of Medicine, and Rush Medical College.
Warren Cole, M.D., F.A.C.S., Professor and Head of the Department of Surgery, University of Illinois College of Medicine.
Arthur R. Colwell, M.D., F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School.
M. Edward Davis, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, University of Chicago.
V. L. Domm, M.D., Research Associate in Zoology, University of Chicago.
Lester Dragstedt, M.D., F.A.C.P., Professor of Surgery, University of Chicago, The School of Medicine.
Earl T. Engle, M.D., Professor of Anatomy, Columbia University College of Physicians and Surgeons, New York.
Frederick Falls, M.D., F.A.C.S., Professor and Head of the Department of Obstetrics and Gynecology, University of Illinois College of Medicine.
Ray Farquharson, M.D., Head of Department of Therapeutics, University of Toronto Faculty of Medicine; Consultant in Medicine to the R.C.A.F.
Morris Fishbein, M.D., Assistant Professor of Medicine, University of Illinois College of Medicine; Editor, Journal of the American Medical Association.
Smith Freeman, M.D., Ph.D., Professor of Physiology, Northwestern University Medical School.
F. X. Gassner, V.M.D., Associate Pathologist, Colorado Experimental Station, Colorado State College, Fort Collins, Colo.

N. C. Gilbert, M.D., F.A.C.P., Professor of Medicine and Head of the Department, Northwestern University Medical School.

E. C. Hamblen, M.D., F.A.C.S., Associate Professor of Obstetrics and Gynecology, Department of Obstetrics and Gynecology, Duke University School of Medicine; Chief of Endocrine Division and Endocrinologist, Duke Hospital, Durham, N. C.

Carl G. Hartman, Ph.D., Professor and Head of the Department of Zoology and Physiology, University of Illinois, Urbana.

Norris J. Heckel, M.D., F.A.C.S., Associate Professor of Urology (Rush), University of Illinois College of Medicine.

Don G. Hilldrup, M.D., F.A.C.S., Colonel, (MC), USA, Surgeon, Sixth Service Command, Chicago.

John Eager Howard, M.D., Assistant Professor of Medicine, Johns Hopkins University School of Medicine, and Visiting Physician to the Johns Hopkins Hospital, Baltimore.

Charles Huggins, M.D., Professor of Surgery (Genito-urinary), University of Chicago, The School of Medicine.

Ernest E. Irons, M.D., F.A.C.P., Professor of Medicine, University of Illinois College of Medicine; Regent and President, American College of Physicians.

A. C. Ivy, M.D., F.A.C.P., Nathan Smith Davis Professor of Physiology, Northwestern University Medical School.

Victor Johnson, M.D., Secretary, Council on Medical Education and Hospitals, American Medical Association.

Robert W. Keeton, M.D., F.A.C.P., Professor of Medicine and Head of the Department, University of Illinois College of Medicine.

Edward C. Kendall, M.D., Professor of Biochemistry, Mayo Foundation, University of Minnesota, Rochester, Minn.

Allen T. Kenyon, M.D., Associate Professor of Medicine, University of Chicago, The School of Medicine.

Fred C. Koch, Ph.D., Professor of Biochemistry, Emeritus, University of Chicago.

Cyril M. MacBryde, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Washington University School of Medicine; Director, Metabolism Division, Barnes Hospital; Director, Endocrine and Metabolic Clinics, Washington University Clinics, St. Louis.

Malcolm T. MacEachern, M.D., F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School; Director of Program of Hospital Administration and Associate Director, American College of Surgeons.

Joseph E. Markee, Ph.D., Professor of Anatomy, Duke University School of Medicine, Durham, N. C.

E. Perry McCullagh, M.D., F.A.C.P., Head of Endocrine Research Laboratory, Cleveland Clinic Foundation Hospital, Cleveland, Ohio.

Carl R. Moore, Ph.D., Professor and Head of the Department of Zoology, University of Chicago.

Josiah J. Moore, M.D., F.A.C.P., Director, Moore Clinical Laboratory; Past President, Chicago Medical Society.

Fred H. Muller, M.D., President, Chicago Medical Society.

Warren O. Nelson, M.D., Professor of Anatomy, State University of Iowa College of Medicine, Iowa City.

Rulon W. Rawson, M.D., Associate in Medicine, Harvard Medical School; Assistant in Medicine, Massachusetts General Hospital; Boston.

Henry T. Ricketts, M.D., Associate Professor of Medicine, University of Chicago, The School of Medicine.

Edward H. Rynearson, M.D., F.A.C.P., Associate Professor of Medicine, Mayo Foundation, University of Minnesota, Rochester, Minn.

Lee T. Samuels, Ph.D., Professor of Biochemistry, University of Utah School of Medicine, Salt Lake City.

Elmer L. Sevringhaus, M.D., F.A.C.P., Professor of Medicine, University of Wisconsin Medical School.

E. Kost Shelton, M.D., D.Sc., F.A.C.P., Associate Professor of Medicine, University of Southern California, Los Angeles.

Ephraim Shorr, M.D., Associate Professor of Medicine, Cornell University Medical College; Associate Attending Physician, The New York Hospital; New York.

LeRoy H. Sloan, M.D., F.A.C.P., Professor of Medicine, University of Illinois College of Medicine; Regent, American College of Physicians.

Samuel Soskin, M.D., Ph.D., Professorial Lecturer in Physiology, University of Chicago, The School of Medicine; Medical Director, Michael Reese Hospital.

Kenneth W. Thompson, M.D., Managing Editor of the Journal of Clinical Endocrinology; Clinical Professor of Surgery, Tufts College Medical School; Boston.

Willard O. Thompson, M.D., F.A.C.P., Professor of Medicine (Rush), University of Illinois College of Medicine.

George W. Thorn, M.D., F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School; Physician-in-Chief, The Peter Bent Brigham Hospital; Boston.

Henry H. Turner, M.D., F.A.C.P., Associate Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City.

George E. Wakerlin, M.D., F.A.C.P., Professor of Physiology and Head of the Department, University of Illinois College of Medicine; Associate Dean in charge of the Rush-Presbyterian Division of the University of Illinois College of Medicine.

Outline of Course

Monday, November 5.

Anton J. Carlson, M.D., F.A.C.P., *Presiding*

A.M. Session—Boulevard Room, fifth floor, Hotel Continental.

8:00– 9:00 Registration.

9:00– 9:30 Present Status of Surgical Treatment of Toxic Goiter.
Dr. Cole.

9:30–10:00 Management of Progressive Exophthalmos.
Dr. McCullagh.

10:00–10:30 The Frequent Failure of Continued Thyroid Therapy to Maintain an Increased BMR or Inhibition of Thyroid Function by Prolonged Ingestion of Thyroid Substance.
Dr. Farquharson.

10:30–10:45 Intermission—Refreshments, Gothic Room, third floor.

10:45–11:15 Obesity: An Endocrine Problem?
Dr. Rynearson.

11:15–11:45 Present Status of Thiouracil.
Dr. McCullagh.

11:45–12:15 Addison's Disease.
Dr. Rynearson.

12:15–12:45 Some Physiological Information Desirable in Treating Disorders of the Thyroid.
Dr. Rawson.

12:45– 2:00 Luncheon—Tally-Ho Room, ninth floor.

Victor Johnson, M.D., *Presiding*

P.M. Session—Boulevard Room, fifth floor.

2:00– 2:30 Clinic: Recent Advances in the Treatment of Toxic Goiter.
Dr. W. O. Thompson.

2:30– 3:00 The Parathyroids, Calcium Metabolism and Osteoid Diseases.
Dr. Freeman.
3:00– 3:30 Modern Treatment of Parathyroid Tetany.
Dr. MacBryde.
3:30– 4:00 Present Status of Lipocaic.
Dr. Dragstedt.
4:00– 4:15 Intermission—Refreshments, Gothic Room, third floor.
4:15– 4:45 Endocrine Factors in Progressive Muscular Dystrophy.
Dr. Carey.
4:45– 5:15 Simmonds' Disease: Severe Insufficiency of the Adenohypophysis —Pathological and Clinical Picture.
Dr. Farquharson.
5:15– 5:45 Thyroid Ovarian Relationships.
Dr. Gassner.

Tuesday, November 6.

Ernest E. Irons, M.D., F.A.C.P., *Presiding*

A.M. Session—Boulevard Room, fifth floor.
9:00– 9:30 Nutrition and Hormones.
Dr. Samuels.
9:30–10:00 Controversial Aspects of Diabetes Mellitus.
Dr. Ricketts.
10:00–10:30 The Treatment of Hypogonadism.
Dr. W. O. Thompson.
10:30–10:45 Intermission—Refreshments, Gothic Room, third floor.

Fred H. Muller, M.D., *Presiding*

10:45–11:15 Anomalies of Fat Metabolism in Diabetes Which Lead to Cirrhosis of the Liver.
Dr. Keeton.
11:15–11:45 Improved Forms of Insulin.
Dr. MacBryde.
11:45–12:15 Diagnosis and Treatment of Diabetic Acidosis.
Dr. Colwell.
12:15–12:45 Relations of the Adrenal Cortex to Carbohydrate Metabolism and Work Capacity.
Dr. MacBryde.
12:45– 2:00 Luncheon—Tally-Ho Room, ninth floor.

Raymond B. Allen, M.D., F.A.C.P., *Presiding*

P.M. Session—Boulevard Room, fifth floor.
2:00– 2:30 Islet Cell Tumors and the General Problem of Hypoglycemia.
Dr. Howard.
2:30– 3:00 Occlusion of External Pancreatic Secretion in Man. Results as observed in late follow-up in patients with pancreatoduodenectomy for carcinoma of the head of the pancreas.
Dr. Brunschwig.
3:00– 4:00 The Application of the Vaginal Smear Method to Clinical Endocrinology.
Dr. Shorr.
4:00– 4:15 Intermission—Refreshments, Gothic Room, third floor.
4:15– 4:45 Calcium Metabolism.
Dr. Howard.

4:45– 5:15 Hypometabolism and Hypothyroidism in Children. (Cretinism, Childhood Hypothyroidism and Myxedema, Pituitary Tumor and Adiposogenital Dystrophy).
Dr. McCullagh.
5:15– 5:45 The Endocrines and Diabetes.
Dr. Soskin.

Wednesday, November 7.

N. C. Gilbert, M.D., F.A.C.P., *Presiding*

A.M. Session—Boulevard Room, fifth floor.
9:00– 9:30 The Role of Hormones in Uterine Gland Formation.
Dr. Carl R. Moore.
9:30–10:00 Endocrine Regulation of Menstruation and Menstrual Irregularities.
Dr. Hamblen.
10:00–10:30 Endocrine Basis of Spontaneous Abortion.
Dr. Falls.
10:30–10:45 Intermission—Refreshments, Gothic Room, third floor.

Josiah J. Moore, M.D., F.A.C.P., *Presiding*

10:45–11:15 Disorders of Menstruation.
Dr. Engle.
11:15–11:45 Gonadotropins in the Female.
Dr. Davis.
11:45–12:15 Intersexuality.
Dr. Ivy.
12:15–12:45 Functional Uterine Bleeding.
Dr. William Allen.
12:45– 2:00 Luncheon—Tally-Ho Room, ninth floor.

LeRoy H. Sloan, M.D., F.A.C.P., *Presiding*

P.M. Session—Boulevard Room, fifth floor.
2:00– 2:30 Adolescent Hypovarianism.
Dr. Hamblen.
2:30– 3:00 Anabolic Effects of the Androgens.
Dr. Kenyon.
3:00– 3:30 Morphological Basis for Menstrual Bleeding.
Dr. Markee.
3:30– 4:00 Clinical Aspects of Endometrial Biopsy.
Dr. Hamblen.
4:00– 4:15 Intermission—Refreshments, Gothic Room, third floor.
4:15– 4:45 Treatment of the Menopausal Patient.
Dr. Engle.
4:45– 5:15 Ovarian Development after Attempted Destruction of Cortex.
Dr. Carl R. Moore.
5:15– 5:45 Use of Sex Hormones in the Menopause.
Dr. William Allen.

Thursday, November 8.

Morris Fishbein, M.D., *Presiding*

A.M. Session—Boulevard Room, fifth floor.
9:00– 9:30 Hormonal Relationships of Breast Cancer.
Dr. Huggins.

9:30–10:00 Hormonal Control of Testicular Function.
Dr. Nelson.
10:00–10:30 Endocrine Aspect of Prostatic Cancer.
Dr. Huggins.
10:30–10:45 Intermission—Refreshments, Tropical Room, fifth floor.
10:45–11:15 Endocrine Regulation of Growth.
Dr. W. O. Thompson.
11:15–11:45 Hypoparathyroid Tetany.
Dr. Sevringhaus.
11:45–12:15 Significance of Gonadotropin Assays on Human Urine.
Dr. Koch.
12:15–12:45 The Management of the Obese Patient.
Dr. Shelton.
12:45– 2:00 Luncheon—Tally-Ho Room, ninth floor.

Malcolm T. MacEachern, M.D., F.A.C.P., *Presiding*

P.M. Session—Boulevard Room, fifth floor.
2:00– 2:30 Eight Years of Clinical Experience with Testosterone Propionate.
Dr. Turner.
2:30– 3:00 Studies on Experimental Cryptorchidism.
Dr. Nelson.
3:00– 3:30 The Management of the Menopause.
Dr. Shorr.
3:30– 4:00 The Diagnosis and Management of Male Infertility.
Dr. Heckel.
4:00– 4:15 Intermission—Refreshments, Tropical Room, fifth floor.
4:15– 4:45 Treatment of Sterility.
Dr. Engle.
4:45– 5:15 The Role of Hormones in Sexual Behavior.
Dr. Domm.
5:15– 5:45 Management of the Climacteric, Male or Female.
Dr. Sevringhaus.

Friday, November 9.

George E. Wakerlin, M.D., F.A.C.P., *Presiding*

A.M. Session—Boulevard Room, fifth floor.
9:00– 9:30 Anorexia Nervosa.
Dr. Keeton.
9:30–10:00 Endocrine Therapy in Certain Urological Diseases.
Dr. Heckel.
10:00–10:30 Types of Endocrine Dwarfism.
Dr. Kenyon.
10:30–10:45 Intermission—Refreshments, Tropical Room, fifth floor.
10:45–11:15 Endocrine Factors in Adolescence.
Dr. Nelson.
11:15–11:45 Thyrotoxic Myopathy.
Dr. Thorn.
11:45–12:15 Problems of Growth and Development.
Dr. Shelton.
12:15–12:45 Treatment of Addison's Disease.
Dr. W. O. Thompson.
12:45– 2:00 Luncheon—Tally-Ho Room, ninth floor.

Don G. Hilldrup, Colonel, (MC), USA, *Presiding*

P.M. Session—Boulevard Room, fifth floor.

2:00– 2:30 Diagnosis and Treatment of Adrenal Insufficiency.
Dr. Thorn.

2:30– 3:00 The Cushing Syndrome.
Dr. Kenneth W. Thompson.

3:00– 3:30 The Significance of 17 Keto-Steroid and Other Steroid Excretion in Man.
Dr. Koch.

3:30– 4:00 Persistence of Estrogenic Effects.
Dr. Turner.

4:00– 4:15 Intermission—Refreshments, Tropical Room, fifth floor.

4:15– 4:45 The Use and Abuse of the Dextrose Tolerance Test.
Dr. Soskin.

4:45– 5:15 The Influence of the Adrenal Cortex on the Metabolism of Sodium, Potassium and Chloride.
Dr. Kendall.

5:15– 5:45 Estrogen Assays, with Particular Reference to a New Test for Blood Estrogens.
Dr. Hartman.

Saturday, November 10.

Joint Session of Postgraduate Course and Regional Meeting of the American College of Physicians.

Hotel Continental

A.M. Session—Tally-Ho Room, ninth floor.

8:00– 9:00 Registration.

9:00 Scientific Session, including the following papers:

Endocrine Causes of Sterility.
Dr. E. C. Hamblen.

Endocrine Regulation of Menstruation.
Dr. Joseph Markee.

Pregnancy Tests, Including a New Six-Hour Method in Which the Male Rat Testis Is Used as Indicator.
Dr. Carl G. Hartman.

Antihormones.
Dr. Kenneth W. Thompson.

Use of Concentrated Human Albumin in the Treatment of Edema of Renal and Hepatic Origin.
Dr. George W. Thorn.

Three or four non-endocrine papers to be announced later.

1:00– 2:30 Luncheon—Boulevard Room, fifth floor.

P.M. Session—Tally-Ho Room, ninth floor.

2:30 Continuation of scientific session of Regional Meeting of the American College of Physicians. Program to be announced later.

5:30– 6:30 Cocktails—Boulevard Room, fifth floor.

6:30 Dinner—Boulevard Room, fifth floor.

COURSE NO. 6—GASTRO-ENTEROLOGY

(November 12–17, 1945)

School of Medicine of the University of Chicago

Dora De Lee Hall

Walter Lincoln Palmer, M.D., F.A.C.P., *Director*

(Minimal Registration, 20; Maximal Registration, 50)

Fee: A.C.P. Members, $20.00; Non-Members, $40.00; Medical Officers (active), Free

Officers of Instruction

William E. Adams, M.D., F.A.C.S., Associate Professor of Surgery, University of Chicago.
J. Garrott Allen, M.D., Instructor in Surgery, University of Chicago.
Robert G. Bloch, M.D., F.A.C.P., Professor of Medicine, University of Chicago.
Alexander Brunschwig, M.D., F.A.C.S., Professor of Surgery, University of Chicago.
Paul R. Cannon, M.D., Professor of Pathology, University of Chicago.
Anton J. Carlson, M.D., F.A.C.P., Professor Emeritus of Physiology, University of Chicago.
Lt. Col. Earl R. Denny, M.D., F.A.C.P., Chief of the Medical Service, Gardiner General Hospital, Chicago.
Lilian Donaldson, M.D., Instructor in Roentgenology, University of Chicago.
Lester R. Dragstedt, M.D., F.A.C.P., Professor of Surgery, University of Chicago.
Jay M. Garner, M.D., F.A.C.P., Instructor in Medicine, Northwestern University Medical School.
Charles W. Hock, M.D., Assistant in Medicine, University of Chicago.
Paul C. Hodges, M.D., Professor of Roentgenology, University of Chicago.
Paul H. Holinger, M.D., Assistant Professor of Laryngology, Rhinology and Otology, University of Illinois.
Eleanor M. Humphreys, M.D., Associate Professor of Pathology, University of Chicago.
Andrew C. Ivy, M.D., F.A.C.P., Professor of Physiology, Northwestern University.
John R. Lindsay, M.D., Professor of Surgery (Otolaryngology), University of Chicago.
Samuel N. Maimon, M.D., Assistant in Medicine, University of Chicago.
Jules H. Masserman, M.D., Assistant Professor of Psychiatry, University of Chicago.
Walter L. Palmer, M.D., F.A.C.P., Professor of Medicine, University of Chicago.
Dallas B. Phemister, M.D., F.A.C.S., Professor of Surgery, University of Chicago.
Henry T. Ricketts, M.D., Associate Professor of Medicine, University of Chicago.
William E. Ricketts, M.D., Assistant in Medicine, University of Chicago.
Stephen Rothman, M.D., Professor of Medicine (Dermatology), University of Chicago.
Gerhart Schwarz, M.D., Instructor in Roentgenology, University of Chicago.
Major Paul L. Shallenberger, M.D., Gardiner General Hospital, Chicago.
David Slight, M.D., Professor of Psychiatry, University of Chicago.
Lowell D. Snorf, M.D., F.A.C.P., Associate Professor of Medicine, Northwestern University.

Location: Dora De Lee Hall of the Chicago Lying-In Hospital, 5841 S. Maryland Avenue, Chicago 37, Illinois.

Luncheon: May be obtained in the Cafeteria in the basement of the Billings Hospital across the street.

Hotel Accommodations: There are at least three first-class hotels located approximately one and one-half miles from the University. Each of these has promised to reserve some rooms for registrants in the Course. However, rooms should be reserved and the reservation confirmed by mail as soon as possible. In writing for reservations, please refer to the American College of Physicians.

The Windermere East Hotel at 1642 East 56th Street (Fairfax 6000) quotes single rooms at $4.00 and $5.00 per day and double rooms at $6.00 and $7.00.

The Del Prado Hotel at 5307 S. Hyde Park Boulevard (Hyde Park 9600) quotes single rooms at $3.50, $4.00 and $5.00 per day and double rooms at $5.00, $6.00 and $7.00.

The Shoreland Hotel at 5454 South Shore Drive (Plaza 1000) quotes single rooms at $5.00 and $6.00 and double rooms at $7.00 and $8.00.

Outline of Course

Monday, November 12.

A.M. Session

8:30– 9:00 Registration: Lying-In Library, Room 173, 5841 Maryland Avenue.
9:00– 9:15 Assembly and Introductory Remarks.
Dr. Palmer.
9:15–10:00 The Hormones of the Digestive Tract.
Dr. Ivy.
10:00–10:40 Nervous Control of the Digestive Tract.
Dr. Carlson.
10:40–11:10 The Role of Amino-acids in the Ingestion of Food.
Dr. Cannon.
11:10–11:20 Intermission.
11:20–12:00 Emotions and the Digestive Tract.
Dr. Slight.
12:00–12:30 Psychogenic Vomiting.
Dr. Masserman.
12:30– 1:00 Migraine and the Digestive Tract.
Dr. Slight.
1:00– 2:00 Lunch.

P.M. Session

2:30– 3:30 Esophagoscopy. (Moving Picture Demonstration.)
Dr. Holinger.
3:30– 3:50 Esophagitis.
Dr. Cannon.
3:50– 4:00 Intermission.
4:00– 4:25 X-Ray Examination of the Esophagus.
Dr. Schwarz.
4:25– 4:45 Esophageal Varices.
Dr. Lindsay.
4:45– 5:30 Benign Stricture of the Esophagus.
Dr. Palmer.

Tuesday, November 13.

A.M. Session

9:00– 9:30 Scleroderma and Esophageal Stricture.
Drs. Rothman and Lindsay.
9:30–10:00 Morphology of Esophageal Carcinoma.
Dr. Humphreys.
10:00–10:30 Surgical Treatment of Esophageal Carcinoma.
Dr. Adams.

10:30–10:50 Radiation Therapy of Esophageal Carcinoma.
Dr. Hock.
10:50–11:00 Intermission.
11:00–11:30 Surgical Treatment of Benign Lesions of the Esophagus.
Dr. Adams.
11:30– 1:00 Cardiospasm, with case demonstrations.
Dr. Palmer.
1:00– 2:00 Lunch.

P.M. Session

2:00– 2:30 Gastric Analysis.
Dr. Palmer.
2:30–2:50 The Technique of the Gastro-duodenal X-Ray Examination.
Dr. Hodges.
2:50– 3:30 Gastroscopy and Gastritis.
Dr. Maimon.
3:30– 4:00 An Evaluation of Gastroscopy and X-Ray.
Dr. William E. Ricketts.
4:00– 4:10 Intermission.
4:10– 4:40 Tumor Forming Gastritis.
Dr. Maimon.
4:40– 5:00 Gastritis and Dyspepsia.
Dr. Palmer.

Wednesday, November 14.

A.M. Session—PEPTIC ULCER

9:00–10:00 Pathogenesis and Pain Mechanism.
Dr. Palmer.
10:00–10:30 X-Ray Manifestations
Dr. Donaldson.
10:30–11:20 Medical Treatment.
Dr. Palmer.
11:20–11:30 Intermission.
11:30–12:15 Surgical Treatment.
Dr. Dragstedt.
12:15– 1:00 Treatment of the Complications.
Dr. Palmer.
1:00– 2:00 Lunch.

P.M. Session

2:00– 3:00 Pathogenesis of Gastric Cancer.
Dr. Palmer.
3:00– 3:20 X-Ray Manifestations.
Dr. Hodges.
3:20– 3:45 Gastroscopic Aspects.
Dr. William E. Ricketts.
3:45– 3:55 Intermission.
3:55– 4:30 The Life History of Gastric Cancer.
Dr. Palmer.
4:30– 5:30 Surgical Treatment of Gastric Cancer.
Dr. Brunschwig.

Thursday, November 15.

A.M. Session

9:00– 9:30 The Results of Surgical Treatment of Gastric Cancer.
Dr. Maimon.
9:30–10:00 Peptic Digestion in Gastric Malignancy.
Dr. Palmer.

10:00–10:50 Physiology of the Liver.
Dr. Ivy.
10:50–11:00 Intermission.
11:00–11:30 Liver in Relation to Serum Protein Formation.
Dr. Humphreys.
11:30–12:00 Hepatic Function Tests.
Dr. Allen.
12:00–12:40 Infectious Hepatitis.
Major Shallenberger.
12:40– 1:00 Toxic Hepatitis.
Dr. Palmer.
1:00– 2:00 Lunch.
P.M. Session
2:00– 2:30 Cholelithiasis.
Dr. Phemister.
2:30– 3:00 Gall Bladder Dyspepsia.
Dr. Palmer.
3:00–3:40 Surgery of the Pancreas, Liver, and Biliary Ducts.
Dr. Brunschwig.
3:40– 3:50 Intermission.
3:50– 4:15 The Effect of Total Pancreatectomy on Diabetes Mellitus.
Dr. Henry T. Ricketts.
4:15–4:35 Luetic Hepatitis and Splenomegaly (Case Presentation).
Dr. Rothman.
4:35– 5:30 Pathology Conference, Hepatic Cirrhosis.
Drs. Humphreys and Palmer.

Friday, November 16.
A.M. Session
9:00– 9:20 The X-Ray Diagnosis of Small Intestinal Lesions.
Dr. Hodges.
9:20–10:45 Regional Enteritis, with case presentations.
Drs. Dragstedt, Palmer and Hock.
10:45–11:15 Tuberculous Enteritis.
Dr. Bloch.
11:15–11:25 Intermission.
11:25–11:50 Bacillary and Salmonella Infections.
Major Shallenberger.
11:50–12:35 Amebiasis.
Lt. Col. Denny.
12:35– 1:00 Acute Enteritis.
Dr. Palmer.
1:00– 2:00 Lunch.
P.M. Session
2:00– 3:00 Non-specific Ulcerative Colitis, Clinical Picture (Motion Picture Demonstration).
Dr. Snorf.
3:00– 3:30 Complications.
Dr. William E. Ricketts.
3:30– 3:40 Intermission.
3:40– 4:30 Case Presentations.
Drs. Dragstedt, Palmer, and William E. Ricketts.
4:30– 5:30 Proctoscopic Cinematography.
Dr. Garner.

Saturday, November 17.

A.M. Session

9:00– 9:50 Steatorrhea: Case Presentations.
Dr. Henry T. Ricketts.

9:50–10:20 Treatment of Peritonitis Complicating Ulcerative Colitis.
Dr. William E. Ricketts.

10:20–10:50 Radiation Injuries of the Intestine.
Dr. Hock.

10:50–11:00 Intermission.

11:00–11:45 Carcinoma of the Colon.
Dr. Phemister.

11:45–12:15 Pruritus Ani.
Dr. Rothman.

12:15– 1:00 Constipation, Diarrhea, and the Irritable Colon.
Dr. Palmer.

War-Time Graduate Medical Meetings

With the conclusion of the war it is anticipated that the operations of the Committee on War-Time Graduate Medical Meetings will soon terminate. It is proposed, however, to complete all present scheduled programs.

A really fine service to the medical officers in the armed forces has been carried on to a fruitful end. The Central Committee, consisting of Dr. F. F. Borzell, F.A.C.P., Chairman and representative of the American Medical Association, Dr. George Morris Piersol, F.A.C.P., representative of the American College of Physicians, and Dr. Alfred Blalock, F.A.C.S., representative of the American College of Surgeons, deserves the congratulations and appreciation of the medical profession as a whole and of those in the armed services in particular. Thousands of programs covering all the main divisions of medicine and surgery, have been carried on at army and navy installations. Under the original chairmanship of Captain Edward L. Bortz, (MC) U.S.N.R., an efficient nationwide organization was effected. The various zone committees and chairmen and the many members of the faculty who have given of their thought and time are entitled to the plaudits of all.

An extensive two-day program was carried on September 14–15 at the DeWitt General Hospital at Auburn, California. It is not herein published because the meeting has already been concluded.

Other programs scheduled and yet to be given follow:

Region No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. B. P. Widmann, Chairman; Dr. J. S. Rodman, Dr. S. P. Reimann.

U. S. Naval Hospital, Philadelphia, Pennsylvania

October 5—Results of Penicillin Therapy of Syphilis in the European Theater—Colonel Donald M. Pillsbury.

October 26—Recent Advance in the Treatment of Acute Intestinal Obstruction—Dr. E. L. Eliason or Dr. Robert Welty.

Region No. 24 (Southern California)—Lt. Comdr. G. C. Griffith, Chairman; Capt. H. P. Schenck, Dr. J. F. Churchill, Dr. W. A. Morrison, Maj. N. Nixon.

Birmingham General Hospital, Van Nuys, California

September 26—Cardiovascular Problems—Dr. W. Gordon Garnett.

Station Hospital, Camp Cooke, Lompoc, California

September 19—War Wounds of the Chest—Lieutenant Commander J. P. O'Connor and Lieutenant Henry Jaffee.

A.A.F. Regional Station Hospital, March Field, Riverside, California

September 18—The Use of Fibrin and Fibrolysin in Wound Healing—Captain Harry P. Schenck.

A.A.F. Regional and Convalescent Hospital, Santa Ana, California

September 18—Rheumatic Heart Disease—Dr. Louis E. Martin.

Hoff General Hospital, Santa Barbara, California

September 19—War Wounds of the Chest—Lieutenant Commander J. P. O'Connor and Lieutenant Henry Jaffee.

Torney General Hospital, Palm Springs, California

September 18—The Management of the Simple Skin Diseases—Lieutenant Colonel Everett R. Seale.

U. S. Naval Hospital, Santa Margarita Ranch, Oceanside, California

September 27—Differentiation Between the Protozoal and Bacillary Dysenteries—Dr. John F. Kessel.

U. S. Naval Air Training Station, San Diego, California

September 21—The Malingering Tests—Dr. John Mackenzie Brown and Mr. Raymond Brown.

U. S. Naval Hospital, Long Beach, California

September 19—Problems in Tuberculosis—Commander W. L. Rogers.

U. S. Naval Hospital, Corona, California

September 27—The Rh Factor—Captain George Macer.

Merck and Co., Inc., have announced that construction of large manufacturing facilities is being started for the production of streptomycin, a new antibiotic. A production unit consisting of three buildings, including several large fermenters and with 60,000 sq. ft. of floor space, will be constructed at the company's Stonewall Plant at Elkton, Va. A unit for drying and packaging the drug, with 30,000 sq. ft. of floor space, will be constructed at the company's main plant at Rahway, N. J. Total cost will approximate $3,500,000. The new plant is expected to go into production early in 1946.

For many months, Merck has supplied military and other doctors with streptomycin for experimental purposes, from its pilot plant. Clinical study of the many possible uses of streptomycin will be continued as more material becomes available.

Extracted from a mold in much the same manner as penicillin is obtained, streptomycin has activity against certain bacteria which are unaffected by penicillin. In this class are bacteria which cause serious infections of the urinary tract, certain intestinal ailments, and wound infections. Streptomycin already is considered the best known drug for the treatment of tularemia. It has proved highly effective in the treatment of influenzal meningitis, infections due to the Salmonella group, and cystitis caused predominantly by gram-negative organisms. Experiments lead to the hope that it will be useful in the treatment of other diseases, including undulant fever and possibly even tuberculosis.

DDT "Bug Bombs" War on Pacific Insects

DDT-filled Bug Bombs, produced at the rate of more than 1,300,000 a month by Westinghouse alone, are now helping Yanks fight the insect enemy in the Pacific, it was announced by J. H. Ashbaugh, Vice President in charge of the Electric Appliance Division of the Westinghouse Electric Corporation. The "bombs" are produced

at both the Mansfield and East Springfield, Mass., plants of the Company, as well as by other manufacturers.

The Bug Bomb, an insecticide dispenser, is a pint-sized, throw-away container made of light-weight steel from which an aerosol—or mist—is discharged through a valve. The aerosol, using Freon gas as its propellant, now contains DDT.

The entire supply of these "bug bombs" goes to the United States Army for use in planes and ships, and in insect-infested land installations.

Until the recent change-over to DDT, more than 22,000,000 "bombs," containing pyrethrum and sesame oil as the insecticide, had been produced by Westinghouse. In use, however, they were restricted to eradication of malaria-carrying mosquitoes, owing to the limited supply of pyrethrum available. The principal pre-war source of pyrethrum was Japan, although some is grown in other parts of the world.

The Army wanted to permit use of the aerosol "bombs" against such pestiferous and dangerous bugs as flies and lice, and as the pyrethrum supply was not sufficient to permit increasing this ingredient to properly control such insects, DDT, the newly discovered insecticide, was added.

"Now both insect poisons—DDT and pyrethrum—are included in the formula because a combination is more effective against a larger variety of insects than either by itself," Mr. Ashbaugh said.

Some peculiar properties of DDT made it impossible to add it to the old formula without taking these "quirks" into account, Mr. Ashbaugh pointed out. DDT is a powder made with synthetic materials, and is not soluble in water.

The problem in using it in a bomb was to transform it into a liquid, he continued. Therefore, hydrocarbon oil, in which it is soluble, was added to the formula. The oil also helps make the insecticide stick to the insect. Another chemical, cyclohexanone, also helps to dissolve the DDT.

Actually the formula now used in the insecticide contains only about 3 per cent DDT, and approximately 2 per cent pyrethrum, while 85 per cent of it is Freon, the dispensing agent. All of the ingredients—DDT, cyclohexanone, pyrethrum, hydrocarbon oil and Freon—must be controlled rigidly as to quality, weight and volume.

"Cyclohexanone is also 'tricky' to handle because it readily absorbs moisture from the air," Mr. Ashbaugh said. "This makes it necessary to process it by distillation to remove some of this water. It is then pumped into an automatic weighing hopper, as is the DDT, and dumped into a mixing tank. Hydrocarbon oil is added after it also is carefully weighed.

"The ingredients are automatically mixed until they are completely dissolved and then are placed in storage tanks for use. Before the solution is actually put into the 'bombs', however, it is weighed once more in small batches and mixed with pyrethrum extract, which—at about $10 a pound—is the most expensive of the components. The final step is to mix Freon with the other ingredients and the resulting liquid is ready to go into the Bug Bomb."

This insecticidal solution is discharged into the air, where the Freon evaporates. The resulting aerosol is a suspension in the air of tiny particles of highly concentrated insecticide.

Entomologists believe that DDT kills insects in two ways: sometimes it acts internally, being taken into the system during feeding; or it can act as a contact poison which is absorbed by the insect, killing it by paralyzing its nerves. Some insects are affected by DDT in both ways.

OBITUARIES

DR. ARTHUR WEAVER WHITE

Dr. Arthur Weaver White was born June 3, 1877, in Paxton, Illinois, the son of Weaver and Arabella White. He died June 11, 1945.

He received an A.B. degree from Monmouth College, Illinois, in 1898, and an A.M. in 1907. He graduated from Rush Medical College in 1902, and studied in Europe in 1910.

He married Miss Winifred Bushnell on April 29, 1903, who now survives him. His only child, Sherrill Weaver White, is in active service as a Captain in the U.S.M.C.

Dr. White began his active medical career in Oklahoma City in 1905 in the general practice of medicine. He was one of the founders of the Epworth Medical School, which was later taken over by the University of Oklahoma. At the time of his death he was Clinical Professor of Medicine and had had an active teaching career. He was made Emeritus Professor of Medicine in the University on July 1, 1944, but because of the exigencies of war and the absence of so many younger men, he continued his teaching.

He was certified by the American Board of Internal Medicine; a Fellow of the American College of Physicians since 1920; member, Oklahoma City Academy of Medicine; Oklahoma City Internists Association; Honorary member of Pi Beta Pi Medical Fraternity; County, State and American Medical Association. He was on the staff of St. Anthony's Hospital, and Chairman of the Internes Committee.

He was active in his profession up to the day of his death, and had even started to his office when he came back home, and died suddenly of a coronary occlusion.

He was a member of the Men's Dinner Club; Chamber of Commerce; Presbyterian Church; Saddle Club, and was very civic minded. His hobbies were hunting, fishing and horseback riding. He had served as a Captain, M.C., in world War I. He was urbane, meticulous in his profession and his personal appearance.

He was the author of many papers on diseases of the stomach and intestines. He gave most of his attention to his specialty, and was generous of his time and talents on behalf of organized medicine, appearing on many programs in city, state and national gatherings. He drew patients from a vast area, enjoyed a large practice, and was well loved both by his confreres and those in the community in general, and his absence will create a big void.

LEA A. RIELY, M.D., F.A.C.P.,
Governor for Oklahoma

DR. FREDERICK B. MINER

Dr. Frederick Bingham Miner, Fellow of the American College of Physicians since 1924, was born in Bridport, Vermont in 1876, and died at his home in Flint, Michigan, on April 26, 1945.

Following his preparatory training, Dr. Miner took up the study of medicine at the University of Michigan where he remained for two years, then entered the Detroit College of Medicine and Surgery where he received his degree of Doctor of Medicine in 1906.

Deeply interested in neuropsychiatry, Dr. Miner served as a member of the staff of Oak Grove Hospital in Flint, which was under the direction of the late Dr. C. W. Burr, returning to general practice for the next eight years.

When World War I began, Dr. Miner was commissioned into the United States Army and served as a captain from September, 1918 until June, 1919. Upon discharge from the army, he resumed private practice in Flint, Michigan, specializing in pediatrics.

In the year 1921 Dr. Miner was appointed chairman of the committee on endemic goiter of the American Public Health Association, after he advocated the use of iodized salt in the prevention of goiter.

For many years Dr. Miner was a member of the Medical Advisory Board at Women's Hospital, Chief of Pediatric Staff at St. Joseph's Hospital, a member of the General Staff at Hurley Hospital, and Attending Physician at King's Daughters' Foundling Home. He was a Diplomate of the American Board of Pediatrics, Fellow of the American Academy of Pediatrics, a member of the Genesee County and Michigan State Medical Societies, the American Medical Association, and the American Public Health Association.

In addition to his keen interest in medicine, Dr. Miner was a lover of flowers, and he was a trustee and former vice president of the Michigan State Horticultural Society.

The Michigan Fellows and Associates of the American College of Physicians record with deep regret the death of Dr. Miner, a noble and scholarly gentleman, who gave so much to the public service and gave to the practice of Medicine much dignity. His place in the profession will not be easily filled as he leaves many close friends and faithful patients.

Dr. Miner is survived by his wife, Mrs. Katharine Miner, a daughter, Mrs. H. Donald Seller, and a son, Frederick, now serving in the United States Navy.

P. L. Ledwidge, M.D., F.A.C.P.,
Acting Governor for the State of Michigan

DR. ROBERT McNAIR PURDIE

On April 9, 1945, Dr. Robert McNair Purdie, F.A.C.P., of Houston, Texas, died of a subarachnoid hemorrhage. Dr. Purdie was born in

Pocatello, Idaho, on July 4, 1898. His pre-medical training was received at the University of Utah, Salt Lake City, and he attended Northwestern University Medical School in Chicago, Illinois, graduating in 1922. After an internship at Cook County Hospital, he came to Houston, Texas, in 1924, where he devoted his entire time to the practice of Internal Medicine. In 1938 Dr. Purdie was elected a Fellow of the American College of Physicians.

Dr. Purdie was on the Staff of all the hospitals in Houston, taking an active part in all medical affairs. He served as Secretary and later as Vice-President of the Harris County Medical Society. His early death, coming at the height of his medical career, left a host of friends and patients to mourn his passing. He is survived by his wife, a daughter Patricia, and two sons, Robert and Burke, all of Houston.

M. D. Levy, M.D., F.A.C.P.,
Governor for Texas

DR. JESSE HEADEN INMAN

Jesse Headen Inman, an Associate of the College since 1941, died at his home in Bakersfield, California, July 15, 1945, of carcinoma of the colon.

Dr. Inman was born November 25, 1901. He received his A.B. from the University of California in 1925 and his M.D. from the same institution in 1929. He served a residency at the University of Michigan, 1929–30. He was Resident Physician of the Sutter Hospital, Sacramento, 1930–31; Resident Pathologist at the Pennsylvania Hospital, Philadelphia, 1931–32; and Pathologist, Kern General Hospital, 1933–36; since 1938, Pathologist for Mercy Hospital, Bakersfield.

In 1940, Dr. Inman was Vice President of the Kern County Medical Society. He was a member of the California State Medical Society, the California Heart Association, and the American Society of Clinical Pathologists.

The loss of Dr. Inman will be keenly felt by the profession in Bakersfield and vicinity.

Roy E. Thomas, M.D., F.A.C.P.,
Governor for Southern California

DR. JOHN PASCAL SAWYER

Dr. John Pascal Sawyer, F.A.C.P., Emeritus Professor of Clinical Medicine in Western Reserve Medical School, died June 17, 1945, at the age of 83 years. He had been a member of the faculty of the Medical School for 44 years, beginning as a pioneer in the use of the microscope in medical teaching. He was said to have given the first course in laboratory physiology west of the Alleghenies.

Dr. Sawyer, son of a physician, grew up in Cleveland, graduated from Western Reserve's Adelbert College in 1883 and from the Medical Depart-

ment in 1886. Then followed two years of study abroad, especially in physiology in Berlin and Freiburg. He returned as an enthusiastic young teacher and took a leading part in applying the newer scientific methods at Western Reserve Medical School. His clinical interests centered largely around the field of gastro-enterology. He was interested in the organization of the American Gastro-enterological Association, a member in 1900, and its president in 1907. For many years, Dr. Sawyer was known as a leader in this field, which he often referred to as "the most neglected part of medicine and yet the one presenting the greatest therapeutic opportunities."

For half a century, Clevelanders knew Dr. Sawyer as a loyal and kindly private practitioner. He believed in "teaching patients," as well as students, the principles of physiology and personal hygiene. In this respect, he was ahead of his time in the practice of personal preventive medicine.

St. Vincent Charity Hospital was for 37 years the center of Dr. Sawyer's activities and teaching. Many local honors were awarded him during his long career, such as President of the Cleveland Medical Library Association and the degree of Doctor of Humanities from the University in 1941.

For several years, Dr. Sawyer had been in failing health following a cerebral vascular accident, but never lost his kindly interest in people and in medicine. He spent his winters in Vero Beach, Florida. His death came quietly at his old hospital home, "Charity," where he was Emeritus Chief of Staff since 1932.

V. C. Rowland, M.D., F.A.C.P.,
Cleveland, Ohio